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(57) Abstract

The sequences of extended cDNAs encoding secreted proteins are disclosed. The extended cDNAs can be used to express secreted proteins or portions thereof or to obtain antibodies capable of specifically binding to the secreted proteins. The extended cDNAs may also be used in diagnostic, forensic, gene therapy, and chromosome mapping procedures. The extended cDNAs may also be used to design expression vectors and secretion vectors.

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EXTENDED cDNAS for secreted proteins

The present application relates to extended cDNAs which were disclosed in several United States Provisional Patent Applications. Table I lists the SEQ ID Nos. of the extended cDNAs in the present application, the SEQ ID Nos. of the identical or nearly identical extended cDNAs in the provisional applications, and the identities of the provisional applications in which the extended cDNAs were disclosed.

Background of the Invention

The estimated 50,000-100,000 genes scattered along the human chromosomes offer tremendous promise for the understanding, diagnosis, and treatment of human diseases. In addition, probes capable of specifically hybridizing to loci distributed throughout the human genome find applications in the construction of high resolution chromosome maps and in the identification of individuals.

In the past, the characterization of even a single human gene was a painstaking process, requiring years of effort. Recent developments in the areas of cloning vectors, DNA sequencing, and computer technology have merged to greatly accelerate the rate at which human genes can be isolated, sequenced, mapped, and characterized. Cloning vectors such as yeast artificial chromosomes (YACs) and bacterial artificial chromosomes (BACs) are able to accept DNA inserts ranging from 300 to 1000 kilobases (kb) or 100-400 kb in length respectively, thereby facilitating the manipulation and ordering of DNA sequences distributed over great distances on the human chromosomes. Automated DNA sequencing machines permit the rapid sequencing of human genes. Bioinformatics software enables the comparison of nucleic acid and protein sequences, thereby assisting in the characterization of human gene products.

Currently, two different approaches are being pursued for identifying and characterizing the genes distributed
along the human genome. In one approach, large fragments of genomic DNA are isolated, cloned, and sequenced.
Potential open reading frames in these genomic sequences are identified using bio-informatics software. However, this approach entails sequencing large stretches of human DNA which do not encode proteins in order to find the protein encoding sequences scattered throughout the genome. In addition to requiring extensive sequencing, the bio-informatics software may mischaracterize the genomic sequences obtained. Thus, the software may produce false positives in which non-coding DNA is mischaracterized as coding DNA or false negatives in which coding DNA is mislabeled as non-coding DNA.

An alternative approach takes a more direct route to identifying and characterizing human genes. In this approach, complementary DNAs (cDNAs) are synthesized from isolated messenger RNAs (mRNAs) which encode human proteins. Using this approach, sequencing is only performed on DNA which is derived from protein coding portions of the genome. Often, only short stretches of the cDNAs are sequenced to obtain sequences called expressed sequence tags (ESTs). The ESTs may then be used to isolate or purify extended cDNAs which include sequences adjacent to the EST sequences. The extended cDNAs may contain all of the sequence of the EST which was used to obtain them or only a portion of the sequence of the EST which was used to obtain them. In addition, the extended cDNAs may contain the full coding sequence of the gene from which the EST was derived or, alternatively, the extended cDNAs may include

portions of the coding sequence of the gene from which the EST was derived. It will be appreciated that there may be several extended cDNAs which include the EST sequence as a result of alternate splicing or the activity of alternative promoters.

In the past, the short EST sequences which could be used to isolate or purify extended cDNAs were often obtained from oligo-dT primed cDNA libraries. Accordingly, they mainly corresponded to the 3' untranslated region of the mRNA. In part, the prevalence of EST sequences derived from the 3' end of the mRNA is a result of the fact that typical techniques for obtaining cDNAs, are not well suited for isolating cDNA sequences derived from the 5' ends of mRNAs. (Adams et al., Nature 377:174, 1996, Hillier et al., Genome Res. 6:807-828, 1996).

In addition, in those reported instances where longer cDNA sequences have been obtained, the reported sequences typically correspond to coding sequences and do not include the full 5' untranslated region of the mRNA from which the cDNA is derived. Such incomplete sequences may not include the first exon of the mRNA, particularly in situations where the first exon is short. Furthermore, they may not include some exons, often short ones, which are located upstream of splicing sites. Thus, there is a need to obtain sequences derived from the 5' ends of mRNAs which can be used to obtain extended cDNAs which may include the 5' sequences contained in the 5' ESTs.

While many sequences derived from human chromosomes have practical applications, approaches based on the identification and characterization of those chromosomal sequences which encode a protein product are particularly relevant to diagnostic and therapeutic uses. Of the 50,000-100,000 protein coding genes, those genes encoding proteins which are secreted from the cell in which they are synthesized, as well as the secreted proteins themselves, are particularly valuable as potential therapeutic agents. Such proteins are often involved in cell to cell communication and 20 may be responsible for producing a clinically relevant response in their target cells.

In fact, several secretory proteins, including tissue plasminogen activator, G-CSF, GM-CSF, erythropoietin, human growth hormone, insulin, interferon- α , interferon- β , interferon- γ , and interleukin-2, are currently in clinical use. These proteins are used to treat a wide range of conditions, including acute myocardial infarction, acute ischemic stroke, anemia, diabetes, growth hormone deficiency, hepatitis, kidney carcinoma, chemotherapy induced neutropenia and 25 multiple sclerosis. For these reasons, extended cDNAs encoding secreted proteins or portions thereof represent a particularly valuable source of therapeutic agents. Thus, there is a need for the identification and characterization of secreted proteins and the nucleic acids encoding them.

In addition to being therapeutically useful themselves, secretory proteins include short peptides, called signal peptides, at their amino termini which direct their secretion. These signal peptides are encoded by the signal sequences 30 located at the 5' ends of the coding sequences of genes encoding secreted proteins. Because these signal peptides will direct the extracellular secretion of any protein to which they are operably linked, the signal sequences may be exploited to direct the efficient secretion of any protein by operably linking the signal sequences to a gene encoding the protein for which secretion is desired. This may prove beneficial in gene therapy strategies in which it is desired to deliver a particular gene product to cells other than the cell in which it is produced. Signal sequences encoding signal peptides

also find application in simplifying protein purification techniques. In such applications, the extracellular secretion of the desired protein greatly facilitates purification by reducing the number of undesired proteins from which the desired protein must be selected. Thus, there exists a need to identify and characterize the 5' portions of the genes for secretory proteins which encode signal peptides.

Public information on the number of human genes for which the promoters and upstream regulatory regions have been identified and characterized is quite limited. In part, this may be due to the difficulty of isolating such regulatory sequences. Upstream regulatory sequences such as transcription factor binding sites are typically too short to be utilized as probes for isolating promoters from human genomic libraries. Recently, some approaches have been developed to isolate human promoters. One of them consists of making a CpG island library (Cross, S.H. et al.,

Purification of CpG Islands using a Methylated DNA Binding Column, Nature Genetics 6: 236-244 (1994)). The second consists of isolating human genomic DNA sequences containing Spel binding sites by the use of Spel binding protein. (Mortlock et al., Genome Res. 6:327-335, 1996). Both of these approaches have their limits due to a lack of specificity or of comprehensiveness.

5' ESTs and extended cDNAs obtainable therefrom may be used to efficiently identify and isolate upstream regulatory regions which control the location, developmental stage, rate, and quantity of protein synthesis, as well as the stability of the mRNA. (Theil et al., BioFactors 4:87-93, (1993). Once identified and characterized, these regulatory regions may be utilized in gene therapy or protein purification schemes to obtain the desired amount and locations of protein synthesis or to inhibit, reduce, or prevent the synthesis of undesirable gene products.

In addition, ESTs containing the 5' ends of secretory protein genes or extended cDNAs which include
sequences adjacent to the sequences of the ESTs may include sequences useful as probes for chromosome mapping and
the identification of individuals. Thus, there is a need to identify and characterize the sequences upstream of the 5'
coding sequences of genes encoding secretory proteins.

Summary of the Invention

The present invention relates to purified, isolated, or recombinant extended cDNAs which encode secreted proteins or fragments thereof. Preferably, the purified, isolated or recombinant cDNAs contain the entire open reading frame of their corresponding mRNAs, including a start codon and a stop codon. For example, the extended cDNAs may include nucleic acids encoding the signal peptide as well as the mature protein. Alternatively, the extended cDNAs may contain a fragment of the open reading frame. In some embodiments, the fragment may encode only the sequence of the mature protein. Alternatively, the fragment may encode only a portion of the mature protein. A further aspect of the present invention is a nucleic acid which encodes the signal peptide of a secreted protein.

The present extended cDNAs were obtained using ESTs which include sequences derived from the authentic 5' ends of their corresponding mRNAs. As used herein the terms "EST" or "5' EST" refer to the short cDNAs which were used to obtain the extended cDNAs of the present invention. As used herein, the term "extended cDNA" refers to the cDNAs which include sequences adjacent to the 5' EST used to obtain them. The extended cDNAs may contain all or a

portion of the sequence of the EST which was used to obtain them. The term "corresponding mRNA" refers to the mRNA which was the template for the cDNA synthesis which produced the 5' EST. As used herein, the term "purified" does not require absolute purity; rather, it is intended as a relative definition. Individual extended cDNA clones isolated from a cDNA library have been conventionally purified to electrophoretic homogeneity. The sequences obtained from these clones could not be obtained directly either from the library or from total human DNA. The extended cDNA clones are not naturally occurring as such, but rather are obtained via manipulation of a partially purified naturally occurring substance (messenger RNA). The conversion of mRNA into a cDNA library involves the creation of a synthetic substance (cDNA) and pure individual cDNA clones can be isolated from the synthetic library by clonal selection. Thus, creating a cDNA library from messenger RNA and subsequently isolating individual clones from that library results in an approximately 10⁴-10⁶ fold purification of the native message. Purification of starting material or natural material to at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated.

As used herein, the term "isolated" requires that the material be removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide present in a living animal is not isolated, but the same polynucleotide, separated from some or all of the coexisting materials in the natural system, is isolated.

As used herein, the term "recombinant" means that the extended cDNA is adjacent to "backbone" nucleic acid to which it is not adjacent in its natural environment. Additionally, to be "enriched" the extended cDNAs will represent 5% or more of the number of nucleic acid inserts in a population of nucleic acid backbone molecules. Backbone molecules according to the present invention include nucleic acids such as expression vectors, self-replicating nucleic acids, viruses, integrating nucleic acids, and other vectors or nucleic acids used to maintain or manipulate a nucleic acid insert of interest. Preferably, the enriched extended cDNAs represent 15% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. More preferably, the enriched extended cDNAs represent 50% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. In a highly preferred embodiment, the enriched extended cDNAs represent 90% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. "Stringent", "moderate," and "low" hybridization conditions are as defined in Example 29.

Unless otherwise indicated, a "complementary" sequence is fully complementary. Thus, extended cDNAs encoding secreted polypeptides or fragments thereof which are present in cDNA libraries in which one or more extended cDNAs encoding secreted polypeptides or fragments thereof make up 5% or more of the number of nucleic acid inserts in the backbone molecules are "enriched recombinant extended cDNAs" as defined herein. Likewise, extended cDNAs encoding secreted polypeptides or fragments thereof which are in a population of plasmids in which one or more extended cDNAs of the present invention have been inserted such that they represent 5% or more of the number of inserts in the plasmid backbone are "enriched recombinant extended cDNAs" as defined herein. However, extended

cDNAs encoding secreted polypeptides or fragments thereof which are in cDNA libraries in which the extended cDNAs encoding secreted polypeptides or fragments thereof constitute less than 5% of the number of nucleic acid inserts in the population of backbone molecules, such as libraries in which backbone molecules having a cDNA insert encoding a secreted polypeptide are extremely rare, are not "enriched recombinant extended cDNAs."

In particular, the present invention relates to extended cDNAs which were derived from genes encoding secreted proteins. As used herein, a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal peptides in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g. soluble proteins), or partially (e.g. receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are 10 transported across the membrane of the endoplasmic reticulum.

Extended cDNAs encoding secreted proteins may include nucleic acid sequences, called signal sequences, which encode signal puptides which direct the extracellular secretion of the proteins encoded by the extended cDNAs. Generally, the signal peptides are located at the amino termini of secreted proteins.

Secreted proteins are translated by ribosomes associated with the "rough" endoplasmic reticulum. Generally, 15 secreted proteins are co-translationally transferred to the membrane of the endoplasmic reticulum. Association of the ribosome with the endoplasmic reticulum during translation of secreted proteins is mediated by the signal peptide. The signal peptide is typically cleaved following its co-translational entry into the endoplasmic reticulum. After delivery to the endoplasmic reticulum, secreted proteins may proceed through the Golgi apparatus. In the Golgi apparatus, the proteins may undergo post-translational modification before entering secretory vesicles which transport them across the 20 cell membrane.

The extended cDNAs of the present invention have several important applications. For example, they may be used to express the entire secreted protein which they encode. Alternatively, they may be used to express portions of the secreted protein. The portions may comprise the signal peptides encoded by the extended cDNAs or the mature proteins encoded by the extended cDNAs (i.e. the proteins generated when the signal peptide is cleaved off). The 25 portions may also comprise polypeptides having at least 10 consecutive amino acids encoded by the extended cDNAs. Alternatively, the portions may comprise at least 15 consecutive amino acids encoded by the extended cDNAs. In some embodiments, the portions may comprise at least 25 consecutive amino acids encoded by the extended cDNAs. In other embodiments, the portions may comprise at least 40 amino acids encoded by the extended cDNAs.

Antibodies which specifically recognize the entire secreted proteins encoded by the extended cDNAs or 30 fragments thereof having at least 10 consecutive amino acids, at least 15 consecutive amino acids, at least 25 consecutive amino acids, or at least 40 consecutive amino acids may also be obtained as described below. Antibodies which specifically recognize the mature protein generated when the signal peptide is cleaved may also be obtained as described below. Similarly, antibodies which specifically recognize the signal peptides encoded by the extended cDNAs may also be obtained.

In some embodiments, the extended cDNAs include the signal sequence. In other embodiments, the extended cDNAs may include the full coding sequence for the mature protein (i.e. the protein generated when the signal polypeptide is cleaved off). In addition, the extended cDNAs may include regulatory regions upstream of the translation start site or downstream of the stop codon which control the amount, location, or developmental stage of gene expression. As discussed above, secreted proteins are therapeutically important. Thus, the proteins expressed from the cDNAs may be useful in treating or controlling a variety of human conditions. The extended cDNAs may also be used to obtain the corresponding genomic DNA. The term "corresponding genomic DNA" refers to the genomic DNA which encodes mRNA which includes the sequence of one of the strands of the extended cDNA in which thymidine residues in the sequence of the extended cDNA are replaced by uracil residues in the mRNA.

The extended cDNAs or genomic DNAs obtained therefrom may be used in forensic procedures to identify individuals or in diagnostic procedures to identify individuals having genetic diseases resulting from abnormal expression of the genes corresponding to the extended cDNAs. In addition, the present invention is useful for constructing a high resolution map of the human chromosomes.

The present invention also relates to secretion vectors capable of directing the secretion of a protein of
interest. Such vectors may be used in gene therapy strategies in which it is desired to produce a gene product in one cell
which is to be delivered to another location in the body. Secretion vectors may also facilitate the purification of desired
proteins.

The present invention also relates to expression vectors capable of directing the expression of an inserted gene in a desired spatial or temporal manner or at a desired level. Such vectors may include sequences upstream of the 20 extended cDNAs such as promoters or upstream regulatory sequences.

In addition, the present invention may also be used for gene therapy to control or treat genetic diseases. Signal peptides may also be fused to heterologous proteins to direct their extracellular secretion.

One embodiment of the present invention is a purified or isolated nucleic acid comprising the sequence of one of SEO ID NOs: 40-140 and 242-377 or a sequence complementary thereto. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto. In one aspect of this embodiment, the nucleic acid comprises at least 15, 25, 30, 40, 50, 75, or 100 consecutive bases of one of the sequences of SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto. The nucleic acid may be a recombinant nucleic acid.

Another embodiment of the present invention is a purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent conditions to the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-140 and 242-377. In one aspect of this embodiment, the nucleic acid is recombinant.

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Another embodiment of the present invention is a purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID NOs: 40-140 and 242-377, wherein the full coding sequence optionally comprises the sequence encoding signal peptide as well as the sequence encoding mature protein. In a preferred embodiment, the isolated or purified nucleic acid comprises the full coding sequence of one of SEQ ID Nos. 40, 42-44, 46, 48, 49, 51, 53, 60, 62-72, 76-78, 80-83, 85-88, 90, 93, 94, 97, 99-102, 104, 107-125, 127, 132, 135-138, 140 and 242-377 wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

A further embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEO ID NOs: 40-140 and 242-377 which encode a mature protein. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of one of SEO ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

Yet another embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40·140 and 242·377 which encode the signal peptide. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of SEQ ID NOs: 40, 42·46, 48, 49, 51, 53, 57, 60, 62·73, 76·78, 80·83, 85·88, 90, 93·95, 97, 99·102, 104, 107·125, 127, 128, 130, 132, 134·140 and 242·377 which encode the signal peptide. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

Yet another embodiment of the present invention is a purified or isolated protein comprising the sequence of one of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is a purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the purified or isolated polypeptide comprises at least 15, 20, 25, 35, 50, 75, 100, 150 or 200 consecutive

amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In still another aspect, the purified or isolated polypeptide comprises at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is an isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a signal peptide of one of the polypeptides of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

Yet another embodiment of the present invention is an isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a mature protein of one of the polypeptides of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

A further embodiment of the present invention is a method of making a protein comprising one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 40-140 and 242-377, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the protein encoded by said cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a protein obtainable by the method described in the preceding paragraph.

Another embodiment of the present invention is a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO: 40-140 and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a mature protein obtainable by the method described in the 30 preceding paragraph.

In a preferred embodiment, the above method comprises a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO:

40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto described ~ herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the full coding sequences of one of SEQ ID NOs: 40-140 and 242-377, wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode a mature protein which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEO ID NOs: 40-140 and 242-377 which encode the signal peptide which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEO ID Nos.: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide.

Another embodiment of the present invention is a purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the antibody is capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is an array of cDNAs or fragments thereof of at least 15 nucleotides in length which includes at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides. In one aspect of this embodiment, the array includes at least two of the sequences of SEQ ID NOs: 40-140 and 242-377, the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides. In another aspect of this embodiment, the array includes at least five of the sequences of SEQ ID NOs: 40-140 and 242-377, the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides.

A further embodiment of the invention encompasses purified polynucleotides comprising an insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI or a fragment thereof comprising a contiguous span of at least 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 nucleotides of said insert. An additional embodiment of the invention encompasses purified polypeptides which comprise, consist of, or consist essentially of an amino acid sequence encoded by the insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI, as well as polypeptides which comprise a fragment of said amino acid sequence consisting of a signal peptide, a mature protein, or a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids encoded by said insert.

An additional embodiment of the invention encompasses purified polypeptides which comprise a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids of SEQ ID NOs: 158, 174, 175, 196, 226, 231, 232, wherein said contiguous span comprises at least one of the amino acid positions which was not shown to be identical to a public sequence in any of Figures 11 to 15. Also encompassed by the invention are purified polynuculeotides encoding said polypeptides.

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Brief Description of the Drawings

Figure 1 is a summary of a procedure for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

Figure 2 is an analysis of the 43 amino terminal amino acids of all human SwissProt proteins to determine the frequency of false positives and false negatives using the techniques for signal peptide identification described herein.

Figure 3 shows the distribution of von Heijne scores for 5' ESTs in each of the categories described herein and the probability that these 5' ESTs encode a signal peptide.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the categories described herein were obtained.

Figure 6 illustrates a method for obtaining extended cDNAs.

Figure 7 is a map of pED6dpc2. pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SSt cDNAs are cloned between EcoRI and Notl. PED vectors are described in Kaufman et al. 30 (1991). NAR 19: 4485-4490.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags.

Figure 9 describes the transcription factor binding sites present in each of these promoters.

Figure 10 is an alignment of the protein of SEO ID NO: 217 with the human protein TFAR19 that may play a role in apoptosis (Genbank accession number AF014955, SEO ID NO: 516).

Figure 11 is an alignment of the proteins of SEQ ID NOs: 174, 175 and 232 with a human secreted protein (Genseq accession number W36955, SEQ ID NO: 517).

Figure 12 is an alignment of the protein of SEQ ID NO: 231 with the human E25 protein (Genbank accession number AF038953, SEQ ID NO: 515).

Figure 13 is an alignment of the protein of SEQ ID NO: 196 with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518).

Figure 14 is an alignment of the protein of SEQ ID NOs: 158 with the murine subunit 7a of the COP9 complex 10 (Genbank accession number AF071316, SEQ ID NO: 519).

Figure 15 is an alignment of the protein of SEQ ID NO: 226 with the bovine subunit B14.5B of the NADHubiquinone oxidureductase complex (Arizmendi *et al, FEBS Lett.*, **313**: 80-84 (1992) and Swissprot accession number Q02827, SEQ ID NO: 514).

Detailed Description of the Preferred Embodiment

15 1. Obtaining 5' ESTs

The present extended cDNAs were obtained using 5' ESTs which were isolated as described below.

A. Chemical Methods for Obtaining mRNAs having Intact 5' Ends

In order to obtain the 5' ESTs used to obtain the extended cDNAs of the present invention, mRNAs having intact 5' ends must be obtained. Currently, there are two approaches for obtaining such mRNAs. One of these 20 approaches is a chemical modification method involving derivatization of the 5' ends of the mRNAs and selection of the derivatized mRNAs. The 5' ends of eucaryotic mRNAs possess a structure referred to as a "cap" which comprises a guanosine methylated at the 7 position. The cap is joined to the first transcribed base of the mRNA by a 5', 5'triphosphate bond. In some instances, the 5' guanosine is methylated in both the 2 and 7 positions. Rarely, the 5' guanosine is trimethylated at the 2, 7 and 7 positions. In the chemical method for obtaining mRNAs having intact 5' 25 ends, the 5' cap is specifically derivatized and coupled to a reactive group on an immobilizing substrate. This specific derivatization is based on the fact that only the ribose linked to the methylated guanosine at the 5' end of the mRNA and the ribose linked to the base at the 3' terminus of the mRNA, possess 2', 3'-cis diols. Optionally, where the 3' terminal ribose has a 2', 3'-cis diol, the 2', 3'-cis diol at the 3' end may be chemically modified, substituted, converted, or eliminated, leaving only the ribose linked to the methylated guanosine at the 5' end of the mRNA with a 2', 3'-cis diol. A 30 variety of techniques are available for eliminating the 2', 3'-cis diol on the 3' terminal ribose. For example, controlled alkaline hydrolysis may be used to generate mRNA fragments in which the 3' terminal ribose is a 3'-phosphate, 2'phosphate or (2', 3')-cyclophosphate. Thereafter, the fragment which includes the original 3' ribose may be eliminated from the mixture through chromatography on an oligo-dT column. Alternatively, a base which lacks the 2', 3'-cis diol

may be added to the 3' end of the mRNA using an RNA ligase such as T4 RNA ligase. Example 1 below describes a method for ligation of pCp to the 3' end of messenger RNA.

EXAMPLE 1

Ligation of the Nucleoside Diphosphate pCp to the 3' End of Messenger RNA

1 μg of RNA was incubated in a final reaction medium of 10 μl in the presence of 5 U of T₄ phage RNA ligase in the buffer provided by the manufacturer (Gibco - BRL), 40 U of the RNase inhibitor RNasin (Promega) and, 2 μl of ³²pCp (Amersham #PB 10208).

The incubation was performed at 37°C for 2 hours or overnight at 7-8°C.

Following modification or elimination of the 2', 3'-cis diol at the 3' ribose, the 2', 3'-cis diol present at the 5' end of the mRNA may be oxidized using reagents such as NaBH, NaBH₃CN, or sodium periodate, thereby converting the 2', 3'-cis diol to a dialdehyde. Example 2 describes the oxidation of the 2', 3'-cis diol at the 5' end of the mRNA with sodium periodate.

EXAMPLE 2

Oxidation of 2', 3'-cis diol at the 5' End of the mRNA

- 0.1 OD unit of either a capped oligoribonucleotide of 47 nucleotides (including the cap) or an uncapped oligoribonucleotide of 46 nucleotides were treated as follows. The oligoribonucleotides were produced by in vitro transcription using the transcription kit "AmpliScribe T7" (Epicentre Technologies). As indicated below, the DNA template for the RNA transcript contained a single cytosine. To synthesize the uncapped RNA, all four NTPs were included in the in vitro transcription reaction. To obtain the capped RNA, GTP was replaced by an analogue of the cap, m7G(5')ppp(5')G. This compound, recognized by polymerase, was incorporated into the 5' end of the nascent transcript during the step of initiation of transcription but was not capable of incorporation during the extension step.

 Consequently, the resulting RNA contained a cap at its 5' end. The sequences of the oligoribonucleotides produced by the in vitro transcription reaction were:
 - + Cap:
- 25 5'm7GpppGCAUCCUACUCCCAUCCAAUUCCACCUAACUCCUCCCAUCUCCAC-3' (SEQ ID NO:1)
 - -Can:

5'-pppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3' (SEQ ID NO:2)

The oligoribonucleotides were dissolved in 9 μ l of acetate buffer (0.1 M sodium acetate, pH 5.2) and 3 μ l of freshly prepared 0.1 M sodium periodate solution. The mixture was incubated for 1 hour in the dark at 4°C or room temperature. Thereafter, the reaction was stopped by adding 4 μ l of 10% ethylene glycol. The product was ethanol precipitated, resuspended in 10 μ l or more of water or appropriate buffer and dialyzed against water.

The resulting aldehyde groups may then be coupled to molecules having a reactive amine group, such as hydrazine, carbazide, thiocarbazide or semicarbazide groups, in order to facilitate enrichment of the 5' ends of the mRNAs. Molecules having reactive amine groups which are suitable for use in selecting mRNAs having intact 5' ends

include avidin, proteins, antibodies, vitamins, ligands capable of specifically binding to receptor molecules, or oligonucleotides. Example 3 below describes the coupling of the resulting dialdehyde to biotin.

EXAMPLE.3

Coupling of the Dialdehyde with Biotin

5 The oxidation product obtained in Example 2 was dissolved in 50 μl of sodium acetate at a pH of between 5 and 5.2 and 50 μl of freshly prepared 0.02 M solution of biotin hydrazide in a methoxyethanol/water mixture (1:1) of formula:

In the compound used in these experiments, n=5. However, it will be appreciated that other commercially available hydrazides may also be used, such as molecules of the formula above in which n varies from 0 to 5.

The mixture was then incubated for 2 hours at 37°C. Following the incubation, the mixture was precipitated with ethanol and dialyzed against distilled water.

Example 4 demonstrates the specificity of the biotinylation reaction.

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EXAMPLE 4

Specificity of Biotinylation

The specificity of the biotinylation for capped mRNAs was evaluated by gel electrophoresis of the following samples:

Sample 1. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2 and labeled with ³²pCp as described in Example 1.

Sample 2. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2, labeled with ³²pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.

Sample 3. The 47 nucleotide capped in vitro transcript prepared as in Example 2 and labeled with ³²pCp as described in Example 1.

Sample 4. The 47 nucleotide capped in vitro transcript prepared as in Example 2, labeled with ³²pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.

Samples 1 and 2 had indentical migration rates, demonstrating that the uncapped RNAs were not oxidized and 30 biotinylated. Sample 3 migrated more slowly than Samples 1 and 2, while Sample 4 exhibited the slowest migration.

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The difference in migration of the RNAs in Samples 3 and 4 demonstrates that the capped RNAs were specifically biotinylated.

In some cases, mRNAs having intact 5' ends may be enriched by binding the molecule containing a reactive amine group to a suitable solid phase substrate such as the inside of the vessel containing the mRNAs, magnetic beads, 5 chromatography matrices, or nylon or nitrocellulose membranes. For example, where the molecule having a reactive amine group is biotin, the solid phase substrate may be coupled to avidin or streptavidin. Alternatively, where the molecule having the reactive amine group is an antibody or receptor ligand, the solid phase substrate may be coupled to the cognate antigen or receptor. Finally, where the molecule having a reactive amine group comprises an oligonucleotide, the solid phase substrate may comprise a complementary oligonucleotide.

The mRNAs having intact 5' ends may be released from the solid phase following the enrichment procedure. For example, where the dialdehyde is coupled to biotin hydrazide and the solid phase comprises streptavidin, the mRNAs may be released from the solid phase by simply heating to 95 degrees Celsius in 2% SDS. In some methods, the molecule having a reactive amine group may also be cleaved from the mRNAs having intact 5' ends following enrichment. Example 5 describes the capture of biotinylated mRNAs with streptavidin coated beads and the release of the 15 biotinylated mRNAs from the beads following enrichment.

EXAMPLE 5

Capture and Release of Biotinylated mRNAs Using Strepatividin Coated Beads

The streptavidin-coated magnetic beads were prepared according to the manufacturer's instructions (CPG Inc., USA). The biotinylated mRNAs were added to a hybridization buffer (1.5 M NaCl, pH 5 - 6). After incubating for 30 20 minutes, the unbound and nonbiotinylated material was removed. The beads were washed several times in water with 1% SDS. The beads obtained were incubated for 15 minutes at 95°C in water containing 2% SDS.

Example 6 demonstrates the efficiency with which biotinylated mRNAs were recovered from the streptavidin coated beads.

EXAMPLE 6

Efficiency of Recovery of Biotinylated mRNAs

The efficiency of the recovery procedure was evaluated as follows. RNAs were labeled with 32pCp, oxidized, biotinylated and bound to streptavidin coated beads as described above. Subsequently, the bound RNAs were incubated for 5, 15 or 30 minutes at 95°C in the presence of 2% SDS.

The products of the reaction were analyzed by electrophoresis on 12% polyacrylamide gels under denaturing 30 conditions (7 M urea). The gels were subjected to autoradiography. During this manipulation, the hydrazone bonds were not reduced.

Increasing amounts of nucleic acids were recovered as incubation times in 2% SDS increased, demonstrating that biotinylated mRNAs were efficiently recovered.

In an alternative method for obtaining mRNAs having intact 5' ends, an oligonucleotide which has been derivatized to contain a reactive amine group is specifically coupled to mRNAs having an intact cap. Preferably, the 3' end of the mRNA is blocked prior to the step in which the aldehyde groups are joined to the derivatized oligonucleotide, as described above, so as to prevent the derivatized oligonucleotide from being joined to the 3' end of the mRNA. For example, pCp may be attached to the 3' end of the mRNA using T4 RNA ligase. However, as discussed above, blocking the 3' end of the mRNA is an optional step. Derivatized oligonucleotides may be prepared as described below in Example 7.

EXAMPLE 7

Derivatization of the Oligonucleotide

An oligonucleotide phosphorylated at its 3' end was converted to a 3' hydrazide in 3' by treatment with an aqueous solution of hydrazine or of dihydrazide of the formula H₂N(R1)NH₂ at about 1 to 3 M, and at pH 4.5, in the presence of a carbodiimide type agent soluble in water such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide at a final concentration of 0.3 M at a temperature of 8°C overnight.

The derivatized oligonucleotide was then separated from the other agents and products using a standard technique for isolating oligonucleotides.

As discussed above, the mRNAs to be enriched may be treated to eliminate the 3' OH groups which may be present thereon. This may be accomplished by enzymatic ligation of sequences lacking a 3' OH, such as pCp, as described above in Example 1. Alternatively, the 3' OH groups may be eliminated by alkaline hydrolysis as described in Example 8 below.

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EXAMPLE 8

Alkaline Hydrolysis of mRNA

The mRNAs may be treated with alkaline hydrolysis as follows. In a total volume of 100µl of 0.1N sodium hydroxide, 1.5µg mRNA is incubated for 40 to 60 minutes at 4°C. The solution is neutralized with acetic acid and precipitated with ethanol.

Following the optional elimination of the 3' OH groups, the diol groups at the 5' ends of the mRNAs are oxidized as described below in Example 9.

EXAMPLE 9

Oxidation of Diols

Up to 1 0D unit of RNA was dissolved in 9 μl of buffer (0.1 M sodium acetate, pH 6-7 or water) and 3 μl of freshly prepared 0.1 M sodium periodate solution. The reaction was incubated for 1 h in the dark at 4°C or room temperature. Following the incubation, the reaction was stopped by adding 4 μl of 10% ethylene glycol. Thereafter the mixture was incubated at room temperature for 15 minutes. After ethanol precipitation, the product was resuspended in 10μl or more of water or appropriate buffer and dialyzed against water.

Following oxidation of the diol groups at the 5' ends of the mRNAs, the derivatized oligonucleotide was joined to the resulting aldehydes as described in Example 10.

EXAMPLE 10

Reaction of Aldehydes with Derivatized Oligonucleotides

The oxidized mRNA was dissolved in an acidic medium such as 50 µl of sodium acetate pH 4-6. 50 µl of a solution of the derivatized oligonucleotide was added such that an mRNA:derivatized oligonucleotide ratio of 1:20 was obtained and mixture was reduced with a borohydride. The mixture was allowed to incubate for 2 h at 37°C or overnight (14 h) at 10°C. The mixture was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against distilled water. If desired, the resulting product may be analyzed using acrylamide gel electrophoresis, HPLC analysis, or other conventional techniques.

Following the attachment of the derivatized oligonucleotide to the mRNAs, a reverse transcription reaction may be performed as described in Example 11 below.

EXAMPLE 11

Reverse Transcription of mRNAs

An oligodeoxyribonucleotide was derivatized as follows. 3 OD units of an oligodeoxyribonucleotide of sequence ATCAAGAATTCGCACGAGACCATTA (SEQ ID NO:3) having 5'-OH and 3'-P ends were dissolved in 70 µl of a 1.5 M hydroxybenzotriazole solution, pH 5.3, prepared in dimethylformamide/water (75:25) containing 2 µg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. The mixture was incubated for 2 h 30 min at 22°C. The mixture was then precipitated twice in LiClO₄/acetone. The pellet was resuspended in 200 µl of 0.25 M hydrazine and incubated at 8°C from 3 to 14 h. Following the hydrazine reaction, the mixture was precipitated twice in LiClO₄/acetone.

The messenger RNAs to be reverse transcribed were extracted from blocks of placenta having sides of 2 cm which had been stored at -80°C. The mRNA was extracted using conventional acidic phenol techniques. Oligo-dT chromatography was used to purify the mRNAs. The integrity of the mRNAs was checked by Northern-blotting.

The diol groups on 7 µg of the placental mRNAs were oxidized as described above in Example 9. The derivatized oligonucleotide was joined to the mRNAs as described in Example 10 above except that the precipitation step was replaced by an exclusion chromatography step to remove derivatized oligodeoxyribonucleotides which were not joined to mRNAs. Exclusion chromatography was performed as follows:

10 ml of AcA34 (BioSepra#230151) gel were equilibrated in 50 ml of a solution of 10 mM Tris pH 8.0, 300 mM NaCl, 1 mM EDTA, and 0.05% SDS. The mixture was allowed to sediment. The supernatant was eliminated and the gel was resuspended in 50 ml of buffer. This procedure was repeated 2 or 3 times.

A glass bead (diameter 3 mm) was introduced into a 2 ml disposable pipette (length 25 cm). The pipette was filled with the gel suspension until the height of the gel stabilized at 1 cm from the top of the pipette. The column was then equilibrated with 20 ml of equilibration buffer (10 mM Tris HCl pH 7.4, 20 mM NaCl).

10 μ l of the mRNA which had been reacted with the derivatized oligonucleotide were mixed in 39 μ l of 10 mM urea and 2 μ l of blue-glycerol buffer, which had been prepared by dissolving 5 mg of bromophenol blue in 60% glycerol (v/v), and passing the mixture through a filter with a filter of diameter 0.45 μ m.

The column was loaded. As soon as the sample had penetrated, equilibration buffer was added. 100 µl

fractions were collected. Derivatized oligonucleotide which had not been attached to mRNA appeared in fraction 16 and later fractions. Fractions 3 to 15 were combined and precipitated with ethanol.

The mRNAs which had been reacted with the derivatized oligonucleotide were spotted on a nylon membrane and hybridized to a radioactive probe using conventional techniques. The radioactive probe used in these hybridizations was an oligodeoxyribonucleotide of sequence TAATGGTCTCGTGCGAATTCTTGAT (SEQ ID NO:4) which was anticomplementary to the derivatized oligonucleotide and was labeled at its 5' end with ³²P. 1/10th of the mRNAs which had been reacted with the derivatized oligonucleotide was spotted in two spots on the membrane and the membrane was visualized by autoradiography after hybridization of the probe. A signal was observed, indicating that the derivatized oligonucleotide had been joined to the mRNA.

The remaining 9/10 of the mRNAs which had been reacted with the derivatized oligonucleotide was reverse transcribed as follows. A reverse transcription reaction was carried out with reverse transcriptase following the manufacturer's instructions. To prime the reaction, 50 pmol of nonamers with random sequence were used.

A portion of the resulting cDNA was spotted on a positively charged nylon membrane using conventional methods. The cDNAs were spotted on the membrane after the cDNA:RNA heteroduplexes had been subjected to an alkaline hydrolysis in order to eliminate the RNAs. An oligonucleotide having a sequence identical to that of the derivatized oligonucleotide was labeled at its 5' end with ³²P and hybridized to the cDNA blots using conventional techniques. Single-stranded cDNAs resulting from the reverse transcription reaction were spotted on the membrane. As controls, the blot contained 1 pmol, 100 fmol, 50 fmol, 10 fmol and 1 fmol respectively of a control oligodeoxyribonucleotide of sequence identical to that of the derivatized oligonucleotide. The signal observed in the spots containing the cDNA indicated that approximately 15 fmol of the derivatized oligonucleotide had been reverse transcribed.

These results demonstrate that the reverse transcription can be performed through the cap and, in particular, that reverse transcriptase crosses the 5'-P-P-5' bond of the cap of eukaryotic messenger RNAs.

The single stranded cDNAs obtained after the above first strand synthesis were used as template for PCR reactions. Two types of reactions were carried out. First, specific amplification of the mRNAs for the alpha globin, dehydrogenase, pp15 and elongation factor E4 were carried out using the following pairs of oligodeoxyribonucleotide primers.

alpha-globin

GLO-S: CCG ACA AGA CCA ACG TCA AGG CCG C (SEQ ID NO:5)
GLO-As: TCA CCA GCA GGC AGT GGC TTA GGA G 3' (SEQ ID NO:6)
dehydrogenase

3 DH-S: AGT GAT TCC TGC TAC TTT GGA TGG C (SEQ ID NO:7)

3 DH-As: GCT TGG TCT TGT TCT GGA GTT TAG A (SEQ ID NO:8)

pp15

PP15-S: TCC AGA ATG GGA GAC AAG CCA ATT T (SEQ ID NO:9)

5 PP15-As: AGG GAG GAG GAA ACA GCG TGA GTC C (SEQ ID NO:10)

Elongation factor E4

EFA1-S: ATG GGA AAG GAA AAG ACT CAT ATC A (SEQ ID NO:11)

EF1A-As: AGC AGC AAC AAT CAG GAC AGC ACA G (SEQ ID NO:12)

Non specific amplifications were also carried out with the antisense (_As) oligodeoxyribonucleotides of the 10 pairs described above and a primer chosen from the sequence of the derivatized oligodeoxyribonucleotide (ATCAAGAATTCGCACGAGACCATTA) (SEQ ID NO:13).

A 1.5% agarose gel containing the following samples corresponding to the PCR products of reverse transcription was stained with ethidium bromide. (1/20th of the products of reverse transcription were used for each PCR reaction).

- Sample 1: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the presence of cDNA.
 - Sample 2: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the absence of added cDNA.
- Sample 3: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the presence of cDNA.
 - Sample 4: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the absence of added cDNA.
 - Sample 5: The products of a PCR reaction using the pp15 primers of SEQ ID NOs 9 and 10 in the presence of cDNA.
- Sample 6: The products of a PCR reaction using the pp15 primers of SEQ ID NOs 9 and 10 in the absence of added cDNA.
 - Sample 7: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the presence of added cDNA.
- Sample 8: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the absence of 30 added cDNA.

In Samples 1, 3, 5 and 7, a band of the size expected for the PCR product was observed, indicating the presence of the corresponding sequence in the cDNA population.

PCR reactions were also carried out with the antisense oligonucleotides of the globin and dehydrogenase primers (SEO ID NOs 6 and 8) and an oligonucleotide whose sequence corresponds to that of the derivatized

oligonucleotide. The presence of PCR products of the expected size in the samples corresponding to samples 1 and 3 above indicated that the derivatized oligonucleotide had been incorporated.

The above examples summarize the chemical procedure for enriching mRNAs for those having intact 5' ends.

Further detail regarding the chemical approaches for obtaining mRNAs having intact 5' ends are disclosed in

International Application No. W096/34981, published November 7, 1996.

Strategies based on the above chemical modifications to the 5' cap structure may be utilized to generate cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived. In one version of such procedures, the 5' ends of the mRNAs are modified as described above. Thereafter, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Single stranded RNAs are eliminated to obtain a population of cDNA/mRNA heteroduplexes in which the mRNA includes an intact 5' end. The resulting heteroduplexes may be captured on a solid phase coated with a molecule capable of interacting with the molecule used to derivatize the 5' end of the mRNA. Thereafter, the strands of the heteroduplexes are separated to recover single stranded first cDNA strands which include the 5' end of the mRNA. Second strand cDNA synthesis may then proceed using conventional techniques. For example, the procedures disclosed in WO 96/34981 or in Carninci, P. et al. High-Efficiency Full-Length cDNA Cloning by Biotinylated CAP Trapper. Genomics 37:327-336 (1996) may be employed to select cDNAs which include the sequence derived from the 5' end of the coding sequence of the mRNA.

Following ligation of the oligonucleotide tag to the 5' cap of the mRNA, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Following elimination of the RNA component of the resulting heteroduplex using standard techniques, second strand cDNA synthesis is conducted with a primer complementary to the oligonucleotide tag.

Figure 1 summarizes the above procedures for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

B. Enzymatic Methods for Obtaining mRNAs having Intact 5' Ends

Other techniques for selecting cDNAs extending to the 5' end of the mRNA from which they are derived are fully enzymatic. Some versions of these techniques are disclosed in Dumas Milne Edwards J.B. (Doctoral Thesis of Paris VI University, Le clonage des ADNc complets: difficultes et perspectives nouvelles. Apports pour l'etude de la regulation de l'expression de la tryptophane hydroxylase de rat, 20 Dec. 1993), EPO 625572 and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994).

Briefly, in such approaches, isolated mRNA is treated with alkaline phosphatase to remove the phosphate

30 groups present on the 5' ends of uncapped incomplete mRNAs. Following this procedure, the cap present on full length mRNAs is enzymatically removed with a decapping enzyme such as T4 polynucleotide kinase or tobacco acid pyrophosphatase. An oligonucleotide, which may be either a DNA oligonucleotide or a DNA-RNA hybrid oligonucleotide having RNA at its 3' end, is then ligated to the phosphate present at the 5' end of the decapped mRNA using T4 RNA

ligase. The oligonucleotide may include a restriction site to facilitate cloning of the cDNAs following their synthesis. Example 12 below describes one enzymatic method based on the doctoral thesis of Dumas.

EXAMPLE 12

Enzymatic Approach for Obtaining 5' ESTs

Twenty micrograms of PolyA+ RNA were dephosphorylated using Calf Intestinal Phosphatase (Biolabs). After a phenol chloroform extraction, the cap structure of mRNA was hydrolysed using the Tobacco Acid Pyrophosphatase (purified as described by Shinshi et al., Biochemistry 15: 2185-2190, 1976) and a hemi 5'DNA/RNA-3' oligonucleotide having an unphosphorylated 5' end, a stretch of adenosine ribophosphate at the 3' end, and an EcoRI site near the 5' end was ligated to the 5'P ends of mRNA using the T4 RNA ligase (Biolabs). Oligonucleotides suitable for use in this 10 procedure are preferably 30-50 bases in length. Oligonucleotides having an unphosphorylated 5' end may be synthesized by adding a fluorochrome at the 5' end. The inclusion of a stretch of adenosine ribophosphates at the 3' end of the oligonucleotide increases ligation eificiency. It will be appreciated that the oligonucleotide may contain cloning sites other than EcoRI.

Following ligation of the oligonucleotide to the phosphate present at the 5' end of the decapped mRNA, first 15 and second strand cDNA synthesis may be carried out using conventional methods or those specified in EPO 625,572 and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994), and Dumas Milne Edwards, supra. The resulting cDNA may then be ligated into vectors such as those disclosed in Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994) or other nucleic acid vectors known to those skilled in the art using techniques such as those described in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold 20 Spring Harbor Laboratory Press, 1989.

II. Characterization of 5' ESTs

The above chemical and enzymatic approaches for enriching mRNAs having intact 5' ends were employed to obtain 5' ESTs. First, mRNAs were prepared as described in Example 13 below.

EXAMPLE 13

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Preparation of mRNA

Total human RNAs or PolyA+ RNAs derived from 29 different tissues were respectively purchased from LABIMO and CLONTECH and used to generate 44 cDNA libraries as described below. The purchased RNA had been isolated from cells or tissues using acid guanidium thiocyanate-phenol-chloroform extraction (Chomczyniski, P and Sacchi, N., Analytical Biochemistry 162:156-159, 1987). PolyA+ RNA was isolated from total RNA (LABIMO) by 30 two passes of oligodT chromatography, as described by Aviv and Leder (Aviv, H. and Leder, P., Proc. Natl. Acad. Sci. USA 69:1408-1412, 1972) in order to eliminate ribosomal RNA.

The quality and the integrity of the poly A+ were checked. Northern blots hybridized with a globin probe were used to confirm that the mRNAs were not degraded. Contamination of the PolyA+ mRNAs by ribosomal sequences was checked using RNAs blots and a probe derived from the sequence of the 28S RNA. Preparations of mRNAs with less

than 5% of ribosomal RNAs were used in library construction. To avoid constructing libraries with RNAs contaminated by exogenous sequences (prokaryotic or fungal), the presence of bacterial 16S ribosomal sequences or of two highly expressed mRNAs was examined using PCR.

Following preparation of the mRNAs, the above described chemical and/or the enzymatic procedures for enriching mRNAs having intact 5' ends discussed above were employed to obtain 5' ESTs from various tissues. In both approaches an oligonucleotide tag was attached to the cap at the 5' ends of the mRNAs. The oligonucleotide tag had an EcoRI site therein to facilitate later cloning procedures.

Following attachment of the oligonucleotide tag to the mRNA by either the chemical or enzymatic methods, the integrity of the mRNA was examined by performing a Northern blot with 200-500ng of mRNA using a probe

10 complementary to the oligonucleotide tag.

EXAMPLE 14

cDNA Synthesis Using mRNA Templates Having Intact 5' Ends

For the mRNAs joined to oligonucleotide tags using both the chemical and enzymatic methods, first strand cDNA synthesis was performed using reverse transcriptase with random nonamers as primers. In order to protect internal EcoRI sites in the cDNA from digestion at later steps in the procedure, methylated dCTP was used for first strand synthesis. After removal of RNA by an alkaline hydrolysis, the first strand of cDNA was precipitated using isopropanol in order to eliminate residual primers.

For both the chemical and the enzymatic methods, the second strand of the cDNA was synthesized with a Klenow fragment using a primer corresponding to the 5'end of the ligated oligonucleotide described in Example 12.

Preferably, the primer is 20-25 bases in length. Methylated dCTP was also used for second strand synthesis in order to protect internal EcoRI sites in the cDNA from digestion during the cloning process.

Following cDNA synthesis, the cDNAs were cloned into pBlueScript as described in Example 15 below.

EXAMPLE 15

Insertion of cDNAs into BlueScript

Following second strand synthesis, the ends of the cDNA were blunted with T4 DNA polymerase (Biolabs) and the cDNA was digested with EcoRI. Since methylated dCTP was used during cDNA synthesis, the EcoRI site present in the tag was the only site which was hemi-methylated. Consequently, only the EcoRI site in the oligonucleotide tag was susceptible to EcoRI digestion. The cDNA was then size fractionated using exclusion chromatography (AcA, Biosepra). Fractions corresponding to cDNAs of more than 150 bp were pooled and ethanol precipitated. The cDNA was directionally cloned into the Smal and EcoRI ends of the phagemid pBlueScript vector (Stratagene). The ligation mixture was electroporated into bacteria and propagated under appropriate antibiotic selection.

Clones containing the oligonucleotide tag attached were selected as described in Example 16 below.

EXAMPLE 16

Selection of Clones Having the Oligonucleotide Tag Attached Thereto

The plasmid DNAs containing 5' EST libraries made as described above were purified (Qiagen). A positive selection of the tagged clones was performed as follows. Briefly, in this selection procedure, the plasmid DNA was converted to single stranded DNA using gene II endonuclease of the phage F1 in combination with an exonuclease (Chang et al., Gene 127:95-8, 1993) such as exonuclease III or T7 gene 6 exonuclease. The resulting single stranded DNA was then purified using paramagnetic beads as described by Fry et al., Biotechniques, 13: 124-131, 1992. In this procedure, the single stranded DNA was hybridized with a biotinylated oligonucleotide having a sequence corresponding to the 3' end of the oligonucleotide described in Example 13. Preferably, the primer has a length of 20-25 bases. Clones including a sequence complementary to the biotinylated oligonucleotide were captured by incubation with streptavidin coated magnetic beads followed by magnetic selection. After capture of the positive clones, the plasmid DNA was released from the magnetic beads and converted into double stranded DNA using a DNA polymerase such as the ThermoSequenase obtained from Amersham Pharmacia Biotech. Alternatively, protocols such as the Gene Trapper kit (Gibco BRL) may be used. The double stranded DNA was then electroporaved into bacteria. The percentage of positive clones having the 5' tag oligonucleotide was estimated to typically rank between 90 and 98% using dot blot analysis.

Following electroporation, the libraries were ordered in 384-microtiter plates (MTP). A copy of the MTP was stored for future needs. Then the libraries were transferred into 96 MTP and sequenced as described below.

EXAMPLE 17

Sequencing of Inserts in Selected Clones

Plasmid inserts were first amplified by PCR on PE 9600 thermocyclers (Perkin-Elmer), using standard SETA-A and SETA-B primers (Genset SA), AmpliTaqGold (Perkin-Elmer), dNTPs (Boehringer), buffer and cycling conditions as recommended by the Perkin-Elmer Corporation.

PCR products were then sequenced using automatic ABI Prism 377 sequencers (Perkin Elmer, Applied Biosystems Division, Foster City, CA). Sequencing reactions were performed using PE 9600 thermocyclers (Perkin Elmer) with standard dye-primer chemistry and ThermoSequenase (Amersham Life Science). The primers used were either T7 or 21M13 (available from Genset SA) as appropriate. The primers were labeled with the JOE, FAM, ROX and TAMRA dyes. The dNTPs and ddNTPs used in the sequencing reactions were purchased from Boehringer. Sequencing buffer, reagent concentrations and cycling conditions were as recommended by Amersham.

Following the sequencing reaction, the samples were precipitated with EtOH, resuspended in formamide loading buffer, and loaded on a standard 4% acrylamide gel. Electrophoresis was performed for 2.5 hours at 3000V on an ABI 377 sequencer, and the sequence data were collected and analyzed using the ABI Prism DNA Sequencing Analysis Software, version 2.1.2.

The sequence data from the 44 cDNA libraries made as described above were transferred to a proprietary database, where quality control and validation steps were performed. A proprietary base-caller ("Trace"), working using a Unix system automatically flagged suspect peaks, taking into account the shape of the peaks, the inter-peak resolution, and the noise level. The proprietary base-caller also performed an automatic trimming. Any stretch of 25 or

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fewer bases having more than 4 suspect peaks was considered unreliable and was discarded. Sequences corresponding to cloning vector or ligation oligonucleotides were automatically removed from the EST sequences. However, the resulting EST sequences may contain 1 to 5 bases belonging to the above mentioned sequences at their 5' end. If needed, these can easily be removed on a case by case basis.

Thereafter, the sequences were transferred to the proprietary NETGENE™ Database for further analysis as described below.

Following sequencing as described above, the sequences of the 5' ESTs were entered in a proprietary database called NETGENETM for storage and manipulation. It will be appreciated by those skilled in the art that the data could be stored and manipulated on any medium which can be read and accessed by a computer. Computer readable media include magnetically readable media, optically readable media, or electronically readable media. For example, the computer readable media may be a hard disc, a floppy disc, a magnetic tape, CD-ROM, RAM, or ROM as well as other types of other media known to those skilled in the art.

In addition, the sequence data may be stored and manipulated in a variety of data processor programs in a variety of formats. For example, the sequence data may be stored as text in a word processing file, such as

MicrosoftWORD or WORDPERFECT or as an ASCII file in a variety of database programs familiar to those of skill in the art, such as DB2, SYBASE, or ORACLE.

The computer readable media on which the sequence information is stored may be in a personal computer, a network, a server or other computer systems known to those skilled in the art. The computer or other system preferably includes the storage media described above, and a processor for accessing and manipulating the sequence data.

Once the sequence data has been stored it may be manipulated and searched to locate those stored sequences which contain a desired nucleic acid sequence or which encode a protein having a particular functional domain. For example, the stored sequence information may be compared to other known sequences to identify homologies, motifs implicated in biological function, or structural motifs.

Programs which may be used to search or compare the stored sequences include the MacPattern (EMBL), BLAST, and BLAST2 program series (NCBI), basic local alignment search tool programs for nucleotide (BLASTN) and peptide (BLASTX) comparisons (Altschul et al, J. Mol. Biol. 215: 403 (1990)) and FASTA (Pearson and Lipman, Proc. Natl. Acad. Sci. USA, 85: 2444 (1988)). The BLAST programs then extend the alignments on the basis of defined match and mismatch criteria.

Motifs which may be detected using the above programs include sequences encoding leucine zippers, helix-turn30 helix motifs, glycosylation sites, ubiquitination sites, alpha helices, and beta sheets, signal sequences encoding signal peptides which direct the secretion of the encoded proteins, sequences implicated in transcription regulation such as homeoboxes, acidic stretches, enzymatic active sites, substrate binding sites, and enzymatic cleavage sites.

Before searching the cDNAs in the NETGENETM database for sequence motifs of interest, cDNAs derived from mRNAs which were not of interest were identified and eliminated from further consideration as described in Example 18 below.

EXAMPLE 18

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Elimination of Undesired Sequences from Further Consideration

5' ESTs in the NETGENE™ database which were derived from undesired sequences such as transfer RNAs, ribosomal RNAs, mitochondrial RNAs, procaryotic RNAs, fungal RNAs, Alu sequences, L1 sequences, or repeat sequences were identified using the FASTA and BLASTN programs with the parameters listed in Table II.

To eliminate 5' ESTs encoding tRNAs from further consideration, the 5' EST sequences were compared to the sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. The comparison was performed using FASTA on both strands of the 5' ESTs. Sequences having more than 80% homology over more than 60 nucleotides were identified as tRNAs. Of the 144,341 sequences screened, 26 were identified as tRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding rRNAs from further consideration, the 5' EST sequences were compared to the sequences of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S = 108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as rRNAs. Of the 144,341 sequences screened, 3,312 were identified as rRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding mtRNAs from further consideration, the 5' EST sequences were compared to the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S = 108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as mtRNAs. Of the 144,341 sequences screened, 6,110 were identified as mtRNAs and eliminated from further consideration.

Sequences which might have resulted from exogenous contaminants were eliminated from further consideration by comparing the 5' EST sequences to release 46 of the EMBL bacterial and fungal divisions using BLASTN with the parameter S = 144. All sequences having more than 90% homology over at least 40 nucleotides were identified as exogenous contaminants. Of the 42 cDNA libraries examined, the average percentages of procaryotic and fungal sequences contained therein were 0.2% and 0.5% respectively. Among these sequences, only one could be identified as a sequence specific to fungi. The others were either fungal or procaryotic sequences having homologies with vertebrate sequences or including repeat sequences which had not been masked during the electronic comparison.

In addition, the 5' ESTs were compared to 6093 Alu sequences and 1115 L1 sequences to mask 5' ESTs containing such repeat sequences from further consideration. 5' ESTs including THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats were also eliminated from further consideration. On average, 11.5% of

the sequences in the libraries contained repeat sequences. Of this 11.5%, 7% contained Alu repeats, 3.3% contained L1 repeats and the remaining 1.2% were derived from the other types of repetitive sequences which were screened. These percentages are consistent with those found in cDNA libraries prepared by other groups. For example, the cDNA libraries of Adams et al. contained between 0% and 7.4% Alu repeats depending on the source of the RNA which was used to prepare the cDNA library (Adams et al., *Nature* 377:174, 1996).

The sequences of those 5' ESTs remaining after the elimination of undesirable sequences were compared with the sequences of known human mRNAs to determine the accuracy of the sequencing procedures described above.

EXAMPLE 19

Measurement of Sequencing Accuracy by Comparison to Known Sequences

To further determine the accuracy of the sequencing procedure described above, the sequences of 5' ESTs derived from known sequences were identified and compared to the known sequences. First, a FASTA analysis with overhangs shorter than 5 bp on both ends was conducted on the 5' ESTs to identify those matching an entry in the public human mRNA database. The 6655 5' ESTs which matched a known human mRNA were then realigned with their cognate mRNA and dynamic programming was used to include substitutions, insertions, and deletions in the list of "errors" which would be recognized. Errors occurring in the last 10 bases of the 5' EST sequences were ignored to avoid the inclusion of spurious cloning sites in the analysis of sequencing accuracy.

This analysis revealed that the sequences incorporated in the NETGENE™ database had an accuracy of more than 99.5%.

To determine the efficiency with which the above selection procedures select cDNAs which include the 5' ends of their corresponding mRNAs, the following analysis was performed.

EXAMPLE 20

Determination of Efficiency of 5' EST Selection

To determine the efficiency at which the above selection procedures isolated 5' ESTs which included sequences close to the 5' end of the mRNAs from which they were derived, the sequences of the ends of the 5' ESTs which were derived from the elongation factor 1 subunit α and ferritin heavy chain genes were compared to the known cDNA sequences for these genes. Since the transcription start sites for the elongation factor 1 subunit α and ferritin heavy chain are well characterized, they may be used to determine the percentage of 5' ESTs derived from these genes which included the authentic transcription start sites.

For both genes, more than 95% of the cDNAs included sequences close to or upstream of the 5' end of the corresponding mRNAs.

To extend the analysis of the reliability of the procedures for isolating 5' ESTs from ESTs in the NETGENE™ database, a similar analysis was conducted using a database composed of human mRNA sequences extracted from GenBank database release 97 for comparison. For those 5' ESTs derived from mRNAs included in the GeneBank database, more than 85% had their 5' ends close to the 5' ends of the known sequence. As some of the mRNA

sequences available in the GenBank database are deduced from genomic sequences, a 5' end matching with these sequences will be counted as an internal match. Thus, the method used here underestimates the yield of ESTs including the authentic 5' ends of their corresponding mRNAs.

The EST libraries made above included multiple 5' ESTs derived from the same mRNA. The sequences of such 5' ESTs were compared to one another and the longest 5' ESTs for each mRNA were identified. Overlapping cDNAs were assembled into continuous sequences (contigs). The resulting continuous sequences were then compared to public databases to gauge their similarity to known sequences, as described in Example 21 below.

EXAMPLE 21

Clustering of the 5' ESTs and Calculation of Novelty Indices for cDNA Libraries

For each sequenced EST library, the sequences were clustered by the 5' end. Each sequence in the library was compared to the others with BLASTN2 (direct strand, parameters S = 107). ESTs with High Scoring Segment Pairs (HSPs) at least 25 bp long, having 95% identical bases and beginning closer than 10 bp from each EST 5' end were grouped. The longest sequence found in the cluster was used as representative of the cluster. A global clustering between libraries was then performed leading to the definition of super-contigs.

To assess the yield of new sequences within the EST libraries, a novelty rate (NR) was defined as: NR = 100 X (Number of new unique sequences found in the library/Total number of sequences from the library). Typically, novelty rating range between 10% and 41% depending on the tissue from which the EST library was obtained. For most of the libraries, the random sequencing of 5' EST libraries was pursued until the novelty rate reached 20%.

Following characterization as described above, the collection of 5' ESTs in NETGENETM was screened to identify those 5' ESTs bearing potential signal sequences as described in Example 22 below.

EXAMPLE 22

Identification of Potential Signal Sequences in 5' ESTs

The 5' ESTs in the NETGENETM database were screened to identify those having an uninterrupted open reading frame (ORF) longer than 45 nucleotides beginning with an ATG codon and extending to the end of the EST.

25 Approximately half of the cDNA sequences in NETGENETM contained such an ORF. The ORFs of these 5' ESTs were searched to identify potential signal motifs using slight modifications of the procedures disclosed in Von Heijne, G. A New Method for Predicting Signal Sequence Cleavage Sites. Nucleic Acids Res. 14:4683-4690 (1986). Those 5' EST sequences encoding a 15 amino acid long stretch with a score of at least 3.5 in the Von Heijne signal peptide identification matrix were considered to possess a signal sequence. Those 5' ESTs which matched a known human mRNA or EST sequence and had a 5' end more than 20 nucleotides downstream of the known 5' end were excluded from further analysis. The remaining cDNAs having signal sequences therein were included in a database called SIGNALTAGTM.

To confirm the accuracy of the above method for identifying signal sequences, the analysis of Example 23 was performed.

EXAMPLE 23

Confirmation of Accuracy of Identification of Potential Signal Sequences in 5' ESTs

The accuracy of the above procedure for identifying signal sequences encoding signal peptides was evaluated by applying the method to the 43 amino terminal amino acids of all human SwissProt proteins. The computed Von Heijne score for each protein was compared with the known characterization of the protein as being a secreted protein or a non-secreted protein. In this manner, the number of non-secreted proteins having a score higher than 3.5 (false positives) and the number of secreted proteins having a score lower than 3.5 (false negatives) could be calculated.

Using the results of the above analysis, the probability that a peptide encoded by the 5' region of the mRNA is in fact a genuine signal peptide based on its Von Heijne's score was calculated based on either the assumption that 10% of human proteins are secreted or the assumption that 20% of human proteins are secreted. The results of this analysis are shown in Figures 2 and 3.

Using the above method of identifying secretory proteins, 5' ESTs for human glucagon, gamma interferon induced monokine precursor, secreted cyclophilin-like protein, human pleiotropin, and human biotinidase precursor all of which are polypeptides which are known to be secreted, were obtained. Thus, the above method successfully identified those 5' ESTs which encode a signal peptide.

To confirm that the signal peptide encoded by the 5' ESTs actually functions as a signal peptide, the signal sequences from the 5' ESTs may be cloned into a vector designed for the identification of signal peptides. Some signal peptide identification vectors are designed to confer the ability to grow in selective medium on host cells which have a signal sequence operably inserted into the vector. For example, to confirm that a 5' EST encodes a genuine signal peptide, the signal sequence of the 5' EST may be inserted upstream and in frame with a non-secreted form of the yeast invertase gene in signal peptide selection vectors such as those described in U.S. Patent No. 5,536,637. Growth of host cells containing signal sequence selection vectors having the signal sequence from the 5' EST inserted therein confirms that the 5' EST encodes a genuine signal peptide.

Alternatively, the presence of a signal peptide may be confirmed by cloning the extended cDNAs obtained using the ESTs into expression vectors such as pXT1 (as described below), or by constructing promoter-signal sequence-reporter gene vectors which encode fusion proteins between the signal peptide and an assayable reporter protein. After introduction of these vectors into a suitable host cell, such as COS cells or NIH 3T3 cells, the growth medium may be harvested and analyzed for the presence of the secreted protein. The medium from these cells is compared to the medium from cells containing vectors lacking the signal sequence or extended cDNA insert to identify vectors which encode a functional signal peptide or an authentic secreted protein.

Those 5' ESTs which encoded a signal peptide, as determined by the method of Example 22 above, were further grouped into four categories based on their homology to known sequences. The categorization of the 5' ESTs is described in Example 24 below.

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Categorization of 5' ESTs Encoding a Signal Peptide

Those 5' ESTs having a sequence not matching any known vertebrate sequence nor any publicly available EST sequence were designated "new." Of the sequences in the SIGNALTAG™ database, 947 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5' ESTs having a sequence not matching any vertebrate sequence but matching a publicly known EST were designated "EST-ext", provided that the known EST sequence was extended by at least 40 nucleotides in the 5' direction. Of the sequences in the SIGNALTAG™ database, 150 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those ESTs not matching any vertebrate sequence but matching a publicly known EST without extending the 10 known EST by at least 40 nucleotides in the 5' direction were designated "EST." Of the sequences in the SIGNALTAG™ database, 599 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5' ESTs matching a human mRNA sequence but extending the known sequence by at least 40 nucleotides in the 5' direction were designated "VERT-ext." Of the sequences in the SIGNALTAG™ database, 23 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category. Included in this category was a 5' EST which 15 extended the known sequence of the human translocase mRNA by more than 200 bases in the 5' direction. A 5' EST which extended the sequence of a human tumor suppressor gene in the 5' direction was also identified.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Each of the 5' ESTs was categorized based on the tissue from which its corresponding mRNA was obtained, 20 as described below in Example 25.

EXAMPLE 25

Categorization of Expression Patterns

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the above described categories were obtained.

In addition to categorizing the 5' ESTs by the tissue from which the cDNA library in which they were first identified was obtained, the spatial and temporal expression patterns of the mRNAs corresponding to the 5' ESTs, as well as their expression levels, may be determined as described in Example 26 below. Characterization of the spatial and temporal expression patterns and expression levels of these mRNAs is useful for constructing expression vectors capable of producing a desired level of gene product in a desired spatial or temporal manner, as will be discussed in more detail 30 below.

In addition, 5' ESTs whose corresponding mRNAs are associated with disease states may also be identified. For example, a particular disease may result from lack of expression, over expression, or under expression of an mRNA corresponding to a 5' EST. By comparing mRNA expression patterns and quantities in samples taken from healthy

individuals with those from individuals suffering from a particular disease, 5' ESTs responsible for the disease may be identified.

It will be appreciated that the results of the above characterization procedures for 5' ESTs also apply to extended cDNAs (obtainable as described below) which contain sequences adjacent to the 5' ESTs. It will also be appreciated that if it is desired to defer characterization until extended cDNAs have been obtained rather than characterizing the ESTs themselves, the above characterization procedures can be applied to characterize the extended cDNAs after their isolation.

EXAMPLE 26

Evaluation of Expression Levels and Patterns of mRNAs

Corresponding to 5' ESTs or Extended cDNAs

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Expression levels and patterns of mRNAs corresponding to 5' ESTs or extended cDNAs (obtainable as described below) may be analyzed by solution hybridization with long probes as described in International Patent Application No. WO 97/05277. Briefly, a 5' EST, extended cDNA, or fragment thereof corresponding to the gene encoding the mRNA to be characterized is inserted at a cloning site immediately downstream of a bacteriophage (T3, T7 or SP6) RNA polymerase promoter to produce antisense RNA. Preferably, the 5' EST or extended cDNA has 100 or more nucleotides. The plasmid is linearized and transcribed in the presence of ribonucleotides comprising modified ribonucleotides (i.e. biotin-UTP and DIG-UTP). An excess of this doubly labeled RNA is hybridized in solution with mRNA isolated from cells or tissues of interest. The hybridizations are performed under standard stringent conditions (40-50°C for 16 hours in an 80% formamide, 0.4 M NaCl buffer, pH 7-8). The unhybridized probe is removed by digestion with ribonucleases specific for single-stranded RNA (i.e. RNases CL3, T1, Phy M, U2 or A). The presence of the biotin-UTP modification enables capture of the hybrid on a microtitration plate coated with streptavidin. The presence of the DIG modification enables the hybrid to be detected and quantified by ELISA using an anti-DIG antibody coupled to alkaline phosphatase.

The 5' ESTs, extended cDNAs, or fragments thereof may also be tagged with nucleotide sequences for the serial analysis of gene expression (SAGE) as disclosed in UK Patent Application No. 2 305 241 A. In this method, cDNAs are prepared from a cell, tissue, organism or other source of nucleic acid for which it is desired to determine gene expression patterns. The resulting cDNAs are separated into two pools. The cDNAs in each pool are cleaved with a first restriction endonuclease, called an "anchoring enzyme," having a recognition site which is likely to be present at least once in most cDNAs. The fragments which contain the 5' or 3' most region of the cleaved cDNA are isolated by binding to a capture medium such as streptavidin coated beads. A first oligonucleotide linker having a first sequence for hybridization of an amplification primer and an internal restriction site for a "tagging endonuclease" is ligated to the digested cDNAs in the first pool. Digestion with the second endonuclease produces short "tag" fragments from the cDNAs.

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A second oligonucleotide having a second sequence for hybridization of an amplification primer and an internal restriction site is ligated to the digested cDNAs in the second pool. The cDNA fragments in the second pool are also digested with the "tagging endonuclease" to generate short "tag" fragments derived from the cDNAs in the second pool. The "tags" resulting from digestion of the first and second pools with the anchoring enzyme and the tagging 5 endonuclease are ligated to one another to produce "ditags." In some embodiments, the ditags are concatamerized to produce ligation products containing from 2 to 200 ditags. The tag sequences are then determined and compared to the sequences of the 5' ESTs or extended cDNAs to determine which 5' ESTs or extended cDNAs are expressed in the cell, tissue, organism, or other source of nucleic acids from which the tags were derived. In this way, the expression pattern of the 5' ESTs or extended cDNAs in the cell, tissue, organism, or other source of nucleic acids is obtained.

Quantitative analysis of gene expression may also be performed using arrays. As used herein, the term array means a one dimensional, two dimensional, or multidimensional arrangement of full length cDNAs (i.e. extended cDNAs which include the coding sequence for the signal peptide, the coding sequence for the mature protein, and a stop codon), extended cDNAs, 5' ESTs or fragments of the full length cDNAs, extended cDNAs, or 5' ESTs of sufficient length to permit specific detection of gene expression. Preferably, the fragments are at least 15 nucleotides in length. More 15 preferably, the fragments are at least 100 nucleotides in length. More preferably, the fragments are more than 100 nucleotides in length. In some embodiments the fragments may be more than 500 nucleotides in length.

For example, quantitative analysis of gene expression may be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in a complementary DNA microarray as described by Schena et al. (Science 270:467-470, 1995; Proc. Natl. Acad. Sci. U.S.A. 93:10614-10619, 1996). Full length cDNAs, extended cDNAs, 5' 20 ESTs or fragments thereof are amplified by PCR and arrayed from 96-well microtiter plates onto silylated microscope slides using high-speed robotics. Printed arrays are incubated in a humid chamber to allow rehydration of the array elements and rinsed, once in 0.2% SDS for 1 min, twice in water for 1 min and once for 5 min in sodium borohydride solution. The arrays are submerged in water for 2 min at 95°C, transferred into 0.2% SDS for 1 min, rinsed twice with water, air dried and stored in the dark at 25°C.

Cell or tissue mRNA is isolated or commercially obtained and probes are prepared by a single round of reverse transcription. Probes are hybridized to 1 cm² microarrays under a 14 x 14 mm glass coverslip for 6-12 hours at 60°C. Arrays are washed for 5 min at 25°C in low stringency wash buffer (1 x SSC/0.2% SDS), then for 10 min at room temperature in high stringency wash buffer (0.1 x SSC/0.2% SDS). Arrays are scanned in 0.1 x SSC using a fluorescence laser scanning device fitted with a custom filter set. Accurate differential expression measurements are obtained by taking the average of the ratios of two independent hybridizations.

Quantitative analysis of the expression of genes may also be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in complementary DNA arrays as described by Pietu et al. (Genome Research 6:492-503, 1996). The full length cDNAs, extended cDNAs, 5' ESTs or fragments thereof are PCR amplified and spotted on membranes. Then, mRNAs originating from various tissues or cells are labeled with radioactive nucleotides. After hybridization and washing in controlled conditions, the hybridized mRNAs are detected by phospho-imaging or autoradiography. Duplicate experiments are performed and a quantitative analysis of differentially expressed mRNAs is then performed.

Alternatively, expression analysis of the 5' ESTs or extended cDNAs can be done through high density

nucleotide arrays as described by Lockhart et al. (Nature Biotechnology 14: 1675-1680, 1996) and Sosnowsky et al.

(Proc. Natl. Acad. Sci. 94:1119-1123, 1997). Oligonucleotides of 15-50 nucleotides corresponding to sequences of the
5' ESTs or extended cDNAs are synthesized directly on the chip (Lockhart et al., *supra*) or synthesized and then
addressed to the chip (Sosnowski et al., *supra*). Preferably, the oligonucleotides are about 20 nucleotides in length.

cDNA probes labeled with an appropriate compound, such as biotin, digoxigenin or fluorescent dye, are

synthesized from the appropriate mRNA population and then randomly fragmented to an average size of 50 to 100 nucleotides. The said probes are then hybridized to the chip. After washing as described in Lockhart et al., *supra* and application of different electric fields (Sosnowsky et al., Proc. Natl. Acad. Sci. 94:1119-1123)., the dyes or labeling compounds are detected and quantified. Duplicate hybridizations are performed. Comparative analysis of the intensity of the signal originating from cDNA probes on the same target oligonucleotide in different cDNA samples indicates a differential expression of the mRNA corresponding to the 5' EST or extended cDNA from which the oligonucleotide sequence has been designed.

III. Use of 5' ESTs to Clone Extended cDNAs and to Clone the Corresponding Genomic DNAs

Once 5' ESTs which include the 5' end of the corresponding mRNAs have been selected using the procedures described above, they can be utilized to isolate extended cDNAs which contain sequences adjacent to the 5' ESTs. The extended cDNAs may include the entire coding sequence of the protein encoded by the corresponding mRNA, including the authentic translation start site, the signal sequence, and the sequence encoding the mature protein remaining after cleavage of the signal peptide. Such extended cDNAs are referred to herein as "full length cDNAs." Alternatively, the extended cDNAs may include only the sequence encoding the mature protein remaining after cleavage of the signal peptide, or only the sequence encoding the signal peptide.

Example 27 below describes a general method for obtaining extended cDNAs. Example 28 below describes the cloning and sequencing of several extended cDNAs, including extended cDNAs which include the entire coding sequence and authentic 5' end of the corresponding mRNA for several secreted proteins.

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The methods of Examples 27, 28, and 29 can also be used to obtain extended cDNAs which encode less than the entire coding sequence of the secreted proteins encoded by the genes corresponding to the 5' ESTs. In some embodiments, the extended cDNAs isolated using these methods encode at least 10 amino acids of one of the proteins encoded by the sequences of SEQ ID NOs: 40-140 and 242-377. In further embodiments, the extended cDNAs encode at least 20 amino acids of the proteins encoded by the sequences of SEQ ID NOs: 40-140 and 242-377. In further embodiments, the extended cDNAs encode at least 30 amino acids of the sequences of SEQ ID NOs: 40-140 and

242-377. In a preferred embodiment, the extended cDNAs encode a full length protein sequence, which includes the protein coding sequences of SEQ ID NOs: 40-140 and 242-377.

EXAMPLE 27

General Method for Using 5' ESTs to Clone and Sequence Extended cDNAs

The following general method has been used to quickly and efficiently isolate extended cDNAs including sequence adjacent to the sequences of the 5' ESTs used to obtain them. This method may be applied to obtain extended cDNAs for any 5' EST in the NETGENETM database, including those 5' ESTs encoding secreted proteins. The method is summarized in Figure 6.

1. Obtaining Extended cDNAs

10 a) First strand synthesis

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The method takes advantage of the known 5' sequence of the mRNA. A reverse transcription reaction is conducted on purified mRNA with a poly 14dT primer containing a 49 nucleotide sequence at its 5' end allowing the addition of a known sequence at the end of the cDNA which corresponds to the 3' end of the mRNA. For example, the primer may have the following sequence: 5'-ATC GTT GAG ACT CGT ACC AGC AGA GTC ACG AGA GAG ACT ACA CGG TAC TGG TTT TTT TTT TTT TTVN -3' (SEQ ID NO:14). Those skilled in the art will appreciate that other sequences may also be added to the poly dT sequence and used to prime the first strand synthesis. Using this primer and a reverse transcriptase such as the Superscript II (Gibco BRL) or Rnase H Minus M-MLV (Promega) enzyme, a reverse transcript anchored at the 3' polyA site of the RNAs is generated.

After removal of the mRNA hybridized to the first cDNA strand by alkaline hydrolysis, the products of the alkaline hydrolysis and the residual poly dT primer are eliminated with an exclusion column such as an AcA34 (Biosepra) matrix as explained in Example 11.

b) Second strand synthesis

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A pair of nested primers on each end is designed based on the known 5' sequence from the 5' EST and the known 3' end added by the poly dT primer used in the first strand synthesis. Software used to design primers are either based on GC content and melting temperatures of oligonucleotides, such as OSP (Illier and Green, *PCR Meth. Appl.* 1:124-128, 1991), or based on the octamer frequency disparity method (Griffais et al., *Nucleic Acids Res.* 19: 3887-3891, 1991 such as PC-Rare (http://bioinformatics.weizmann.ac.il/software/PC-Rare/doc/manuel.html).

Preferably, the nested primers at the 5' end are separated from one another by four to nine bases. The 5' primer sequences may be selected to have melting temperatures and specificities suitable for use in PCR.

Preferably, the nested primers at the 3' end are separated from one another by four to nine bases. For example, the nested 3' primers may have the following sequences: (5'- CCA GCA GAG TCA CGA GAG AGA CTA CAC GG-3'(SEQ ID NO:15), and 5'- CAC GAG AGA GAC TAC ACG GTA CTG G-3' (SEQ ID NO:16). These primers were selected because they have melting temperatures and specificities compatible with their use in PCR. However, those skilled in the art will appreciate that other sequences may also be used as primers.

The first PCR run of 25 cycles is performed using the Advantage Tth Polymerase Mix (Clontech) and the outer primer from each of the nested pairs. A second 20 cycle PCR using the same enzyme and the inner primer from each of the nested pairs is then performed on 1/2500 of the first PCR product. Thereafter, the primers and nucleotides are removed.

5 2. Sequencing of Full Length Extended cDNAs or Fragments Thereof

Due to the lack of position constraints on the design of 5' nested primers compatible for PCR use using the OSP software, amplicons of two types are obtained. Preferably, the second 5' primer is located upstream of the translation initiation codon thus yielding a nested PCR product containing the whole coding sequence. Such a full length extended cDNA undergoes a direct cloning procedure as described in section a below. However, in some cases, the second 5' primer is located downstream of the translation initiation codon, thereby yielding a PCR product containing only part of the ORF. Such incomplete PCR products are submitted to a modified procedure described in section b below.

a) Nested PCR products containing complete ORFs

When the resulting nested PCR product contains the complete coding sequence, as predicted from the 5'EST sequence, it is cloned in an appropriate vector such as pED6dpc2, as described in section 3.

b) Nested PCR products containing incomplete ORFs

When the amplicon does not contain the complete coding sequence, intermediate steps are necessary to obtain both the complete coding sequence and a PCR product containing the full coding sequence. The complete coding sequence can be assembled from several partial sequences determined directly from different PCR products as described in the following section.

Once the full coding sequence has been completely determined, new primers compatible for PCR use are designed to obtain amplicons containing the whole coding region. However, in such cases, 3' primers compatible for PCR use are located inside the 3' UTR of the corresponding mRNA, thus yielding amplicons which lack part of this region, i.e. the polyA tract and sometimes the polyadenylation signal, as illustrated in figure 6. Such full length extended cDNAs are then cloned into an appropriate vector as described in section 3.

c) Sequencing extended cDNAs

Sequencing of extended cDNAs is performed using a Die Terminator approach with the AmpliTaq DNA polymerase FS kit available from Perkin Elmer.

In order to sequence PCR fragments, primer walking is performed using software such as OSP to choose primers and automated computer software such as ASMG (Sutton et al., *Genome Science Technol.* 1: 9-19, 1995) to construct contigs of walking sequences including the initial 5' tag using minimum overlaps of 32 nucleotides. Preferably, primer walking is performed until the sequences of full length cDNAs are obtained.

Completion of the sequencing of a given extended cDNA fragment is assessed as follows. Since sequences located after a polyA tract are difficult to determine precisely in the case of uncloned products, sequencing and primer

walking processes for PCR products are interrupted when a polyA tract is identified in extended cDNAs obtained as described in case b. The sequence length is compared to the size of the nested PCR product obtained as described above. Due to the limited accuracy of the determination of the PCR product size by gel electrophoresis, a sequence is considered complete if the size of the obtained sequence is at least 70 % the size of the first nested PCR product. If the length of the sequence determined from the computer analysis is not at least 70% of the length of the nested PCR product, these PCR products are cloned and the sequence of the insertion is determined. When Northern blot data are available, the size of the mRNA detected for a given PCR product is used to finally assess that the sequence is complete. Sequences which do not fulfill the above criteria are discarded and will undergo a new isolation procedure.

Sequence data of all extended cDNAs are then transferred to a proprietary database, where quality controls 10 and validation steps are carried out as described in example 15.

3. Cloning of Full Length Extended cDNAs

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The PCR product containing the full coding sequence is then cloned in an appropriate vector. For example, the extended cDNAs can be cloned into the expression vector pED6dpc2 (DiscoverEase, Genetics Institute, Cambridge, MA) as follows. The structure of pED6dpc2 is shown in Figure 7. pED6dpc2 vector DNA is prepared with blunt ends by 15 performing an EcoRI digestion followed by a fill in reaction. The blunt ended vector is dephosphorylated. After removal of PCR primers and ethanol precipitation, the PCR product containing the full coding sequence or the extended cDNA obtained as described above is phosphorylated with a kinase subsequently removed by phenol-Sevag extraction and precipitation. The double stranded extended cDNA is then ligated to the vector and the resulting expression plasmid introduced into appropriate host cells.

Since the PCR products obtained as described above are blunt ended molecules that can be cloned in either direction, the orientation of several clones for each PCR product is determined. Then, 4 to 10 clones are ordered in microtiter plates and subjected to a PCR reaction using a first primer located in the vector close to the cloning site and a second primer located in the portion of the extended cDNA corresponding to the 3' end of the mRNA. This second primer may be the antisense primer used in anchored PCR in the case of direct cloning (case a) or the antisense primer located 25 inside the 3'UTR in the case of indirect cloning (case b). Clones in which the start codon of the extended cDNA is operably linked to the promoter in the vector so as to permit expression of the protein encoded by the extended cDNA are conserved and sequenced. In addition to the ends of cDNA inserts, approximately 50 bp of vector DNA on each side of the cDNA insert are also sequenced.

The cloned PCR products are then entirely sequenced according to the aforementioned procedure. In this case, contig assembly of long fragments is then performed on walking sequences that have already contigated for uncloned PCR products during primer walking. Sequencing of cloned amplicons is complete when the resulting contigs include the whole coding region as well as overlapping sequences with vector DNA on both ends.

4. Computer Analysis of Full Length Extended cDNA

Sequences of all full length extended cDNAs are then submitted to further analysis as described below and using the parameters found in Table II with the following modifications. For screening of miscellaneous subdivisions of Genbank, FASTA was used instead of BLASTN and 15 nucleotide of homology was the limit instead of 17. For Alu detection, BLASTN was used with the following parameters: S = 72; identity = 70%; and length = 40 nucleotides.

- Polyadenylation signal and polyA tail which were not search for the 5' ESTs were searched. For polyadenylation signal detection the signal (AATAAA) was searched with one permissible mismatch in the last ten nucleotides preceding the 5' end of the polyA. For the polyA, a stretch of 8 amino acids in the last 20 nucleotides of the sequence was searched with BLAST2N in the sense strand with the following parameters (W = 6, S = 10, E = 1000, and identity = 90%). Finally, patented sequences and ORF homologies were searched using, respectively, BLASTN and BLASTP on GenSEQ
- 10 (Derwent's database of patented nucleotide sequences) and SWISSPROT for ORFs with the following parameters (W = 8 and B = 10). Before examining the extended full length cDNAs for sequences of interest, extended cDNAs which are not of interest are searched as follows.

a) Elimination of undesired sequences

Although 5'ESTs were checked to remove contaminant sequences as described in Example 18, a last verification was carried out to identify extended cDNAs sequences derived from undesired sequences such as vector RNAs, transfer RNAs, ribosomal rRNAs, mitochondrial RNAs, prokaryotic RNAs and fungal RNAs using the FASTA and BLASTN programs on both strands of extended cDNAs as described below.

To identify the extended cDNAs encoding vector RNAs, extended cDNAs are compared to the known sequences of vector RNA using the FASTA program. Sequences of extended cDNAs with more than 90% homology over stretches of 15 nucleotides are identified as vector RNA.

To identify the extended cDNAs encoding tRNAs, extended cDNA sequences were compared to the sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. Sequences of extended cDNAs having more than 80% homology over 60 nucleotides using FASTA were identified as tRNA.

To identify the extended cDNAs encoding rRNAs, extended cDNA sequences were compared to the sequences
of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. Sequences of extended cDNAs having
more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as rRNAs.

To identify the extended cDNAs encoding mtRNAs, extended cDNA sequences were compared to the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. Sequences of extended cDNAs having more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as mtRNAs.

Sequences which might have resulted from other exogenous contaminants were identified by comparing extended cDNA sequences to release 105 of Genbank bacterial and fungal divisions. Sequences of extended cDNAs

having more than 90% homology over 40 nucleotides using BLASTN were identified as exogenous prokaryotic or fungal contaminants.

In addition, extended cDNAs were searched for different repeat sequences, including Alu sequences, L1 sequences, THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats. Sequences of extended cDNAs with more than 70% homology over 40 nucleotide stretches using BLASTN were identified as repeat sequences and masked in further identification procedures. In addition, clones showing extensive homology to repeats, i.e., matches of either more than 50 nucleotides if the homology was at least 75% or more than 40 nucleotides if the homology was at least 90%, were flagged.

b) Identification of structural features

Structural features, e.g. polyA tail and polyadenylation signal, of the sequences of full length extended cDNAs are subsequently determined as follows.

A polyA tail is defined as a homopolymeric stretch of at least 11 A with at most one alternative base within it.

The polyA tail search is restricted to the last 20 nt of the sequence and limited to stretches of 11 consecutive A's because sequencing reactions are often not readable after such a polyA stretch. Stretches with 100% homology over 6 nucleotides are identified as polyA tails.

To search for a polyadenylation signal, the polyA tail is clipped from the full-length sequence. The 50 bp preceding the polyA tail are searched for the canonic polyadenylation AAUAAA signal allowing one mismatch to account for possible sequencing errors and known variation in the canonical sequence of the polyadenylation signal.

c) Identification of functional features

Functional features, e.g. ORFs and signal sequences, of the sequences of full length extended cDNAs were subsequently determined as follows.

The 3 upper strand frames of extended cDNAs are searched for ORFs defined as the maximum length fragments beginning with a translation initiation codon and ending with a stop codon. ORFs encoding at least 20 amino acids are preferred.

Each found ORF is then scanned for the presence of a signal peptide in the first 50 amino-acids or, where appropriate, within shorter regions down to 20 amino acids or less in the ORF, using the matrix method of von Heijne (Nuc. Acids Res. 14: 4683-4690 (1986)) and the modification described in Example 22.

d) Homology to either nucleotidic or proteic sequences

Sequences of full length extended cDNAs are then compared to known sequences on a nucleotidic or proteic 30 basis.

Sequences of full length extended cDNAs are compared to the following known nucleic acid sequences: vertebrate sequences (Genbank), EST sequences (Genbank), patented sequences (Geneseqn) and recently identified sequences (Genbank daily releases) available at the time of filing for the priority documents. Full length cDNA sequences are also compared to the sequences of a private database (Genset internal sequences) in order to find sequences that

have already been identified by applicants. Sequences of full length extended cDNAs with more than 90% homology over 30 nucleotides using either BLASTN or BLAST2N as indicated in Table III are identified as sequences that have already been described. Matching vertebrate sequences are subsequently examined using FASTA; full length extended cDNAs with more than 70% homology over 30 nucleotides are identified as sequences that have already been described.

ORFs encoded by full length extended cDNAs as defined in section c) are subsequently compared to known amino acid sequences found in Swissprot release CHP, PIR release PIR# and Genpept release GPEPT public databases using BLASTP with the parameter W = 8 and allowing a maximum of 10 matches. Sequences of full length extended cDNAs showing extensive homology to known protein sequences are recognized as already identified proteins.

In addition, the three-frame conceptual translation products of the top strand of full length extended cDNAs 10 are compared to publicly known amino acid sequences of Swissprot using BLASTX with the parameter E=0.001. Sequences of full length extended cDNAs with more than 70% homology over 30 amino acid stretches are detected as already identified proteins.

5. Selection of Cloned Full Length Sequences of the Present Invention

Cloned full length extended cDNA sequences that have already been characterized by the aforementioned 15 computer analysis are then submitted to an automatic procedure in order to preselect full length extended cDNAs containing sequences of interest.

a) Automatic sequence preselection

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All complete cloned full length extended cDNAs clipped for vector on both ends are considered. First, a negative selection is operated in order to eliminate unwanted cloned sequences resulting from either contaminants or 20 PCR artifacts as follows. Sequences matching contaminant sequences such as vector RNA, tRNA, mtRNA, rRNA sequences are discarded as well as those encoding ORF sequences exhibiting extensive homology to repeats as defined in section 4 a). Sequences obtained by direct cloning using nested primers on 5' and 3' tags (section 1. case a) but lacking polyA tail are discarded. Only ORFs containing a signal peptide and ending either before the polyA tail (case a) or before the end of the cloned 3'UTR (case b) are kept. Then, ORFs containing unlikely mature proteins such as mature 25 proteins which size is less than 20 amino acids or less than 25% of the immature protein size are eliminated.

In the selection of the OFR, priority was given to the ORF and the frame corresponding to the polypeptides described in SignalTag Patents (United States Patent Application Serial Nos: 08/905,223; 08/905,135; 08/905,051; 08/905,144; 08/905,279; 08/904,468; 08/905,134; and 08/905,133). If the ORF was not found among the OFRs described in the SignalTag Patents, the ORF encoding the signal peptide with the highest score according to Von Heijne method as defined in Example 22 was chosen. If the scores were identical, then the longest ORF was chosen.

Sequences of full length extended cDNA clones are then compared pairwise with BLAST after masking of the repeat sequences. Sequences containing at least 90% homology over 30 nucleotides are clustered in the same class. Each cluster is then subjected to a cluster analysis that detects sequences resulting from internal priming or from

alternative splicing, identical sequences or sequences with several frameshifts. This automatic analysis serves as a basis for manual selection of the sequences.

b) Manual sequence selection

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Manual selection is carried out using automatically generated reports for each sequenced full length extended cDNA clone. During this manual procedures, a selection is operated between clones belonging to the same class as follows. ORF sequences encoded by clones belonging to the same class are aligned and compared. If the homology between nucleotidic sequences of clones belonging to the same class is more than 90% over 30 nucleotide stretches or if the homology between amino acid sequences of clones belonging to the same class is more than 80% over 20 amino acid stretches, than the clones are considered as being identical. The chosen ORF is the best one according to the criteria mentioned below. If the nucleotide and amino acid homologies are less than 90% and 80% respectively, the clones are said to encode distinct proteins which can be both selected if they contain sequences of interest.

Selection of full length extended cDNA clones encoding sequences of interest is performed using the following criteria. Structural parameters (initial tag, polyadenylation site and signal) are first checked. Then, homologies with known nucleic acids and proteins are examined in order to determine whether the clone sequence match a known nucleic/proteic sequence and, in the latter case, its covering rate and the date at which the sequence became public. If there is no extensive match with sequences other than ESTs or genomic DNA, or if the clone sequence brings substantial new information, such as encoding a protein resulting from alternative slicing of an mRNA coding for an already known protein, the sequence is kept. Examples of such cloned full length extended cDNAs containing sequences of interest are described in Example 28. Sequences resulting from chimera or double inserts as assessed by homology to other sequences are discarded during this procedure.

EXAMPLE 28

Cloning and Sequencing of Extended cDNAs

The procedure described in Example 27 above was used to obtain the extended cDNAs of the present invention. Using this approach, the full length cDNA of SEQ ID NO:17 was obtained. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MKKVLLLITAILAVAVG (SEQ ID NO: 18) having a von Heijne score of 8.2.

The full length cDNA of SEQ ID NO:19 was also obtained using this procedure. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MWWFQQGLSFLPSALVIWTSA (SEQ ID NO:20) having a von Heijne score of 5.5.

Another full length cDNA obtained using the procedure described above has the sequence of SEQ ID NO:21.

This cDNA, falls into the "EST-ext" category described above and encodes the signal peptide

MVLTTLPSANSANSPVNMPTTGPNSLSYASSALSPCLT (SEQ ID NO:22) having a von Heijne score of 5.9.

The above procedure was also used to obtain a full length cDNA having the sequence of SEQ ID NO:23. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide ILSTVTALTFAXA (SEQ ID NO:24) having a von Heijne score of 5.5.

The full length cDNA of SEQ ID NO:25 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LVLTLCTLPLAVA (SEQ ID NO:26) having a von Heijne score of 10.1.

The full length cDNA of SEQ ID NO:27 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LWLLFFLVTAIHA (SEQ ID NO:28) having a von Heijne score of 10.7.

The above procedures were also used to obtain the extended cDNAs of the present invention. 5' ESTs expressed in a variety of tissues were obtained as described above. The appended sequence listing provides the tissues from which the extended cDNAs were obtained. It will be appreciated that the extended cDNAs may also be expressed in tissues other than the tissue listed in the sequence listing.

5' ESTs obtained as described above were used to obtain extended cDNAs having the sequences of SEQ ID

NOs: 40-140 and 242-377. Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-140 and 242-377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of stop codons (listed under the heading Stop Codon Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of polyA signals (listed under the heading Poly A Signal Location in Table IV) and the locations of polyA sites (listed under the heading Poly A Site Location in Table IV).

The polypeptides encoded by the extended cDNAs were screened for the presence of known structural or functional motifs or for the presence of signatures, small amino acid sequences which are well conserved amongst the members of a protein family. The conserved regions have been used to derive consensus patterns or matrices included in the PROSITE data bank, in particular in the file prosite.dat (Release 13.0 of November 1995, located at http://expasy.hcuge.ch/sprot/prosite.html. Prosite_convert and prosite_scan programs (http://ulrec3.unil.ch/ftpserveur/prosite_scan) were used to find signatures on the extended cDNAs.

For each pattern obtained with the prosite_convert program from the prosite.dat file, the accuracy of the detection on a new protein sequence has been tested by evaluating the frequency of irrelevant hits on the population of human secreted proteins included in the data bank SWISSPROT. The ratio between the number of hits on shuffled proteins (with a window size of 20 amino acids) and the number of hits on native (unshuffled) proteins was used as an index. Every pattern for which the ration was greater than 20% (one hit on shuffled proteins for 5 hits on native

proteins) was skipped during the search with prosite_scan. The program used to shuffle protein sequences (db_shuffled) and the program used to determine the statistics for each pattern in the protein data banks (prosite statistics) are available on the ftp site http://ulrec3.unil.ch/ftpserveur/prosite scan.

Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 141-241 and 378-513, the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the mature polypeptide created by cleaving the signal peptide from the full length polypeptide (fourth column).

The nucleotide sequences of the sequences of SEQ ID NOs: 40-140 and 242-377 and the amino acid sequences

10 encoded by SEQ ID NOs: 40-140 and 242-377 (i.e. amino acid sequences of SEQ ID NOs: 141-241 and 378-513) are

provided in the appended sequence listing. In some instances, the sequences are preliminary and may include some
incorrect or ambiguous sequences or amino acids. The sequences of SEQ ID NOs: 40-140 and 242-377 can readily be
screened for any errors therein and any sequence ambiguities can be resolved by resequencing a fragment containing
such errors or ambiguities on both strands. Nucleic acid fragments for resolving sequencing errors or ambiguities may be
obtained from the deposited clones or can be isolated using the techniques described herein. Resolution of any such
ambiguities or errors may be facilitated by using primers which hybridize to sequences located close to the ambiguous or
erroneous sequences. For example, the primers may hybridize to sequences within 50-75 bases of the ambiguity or
error. Upon resolution of an error or ambiguity, the corresponding corrections can be made in the protein sequences
encoded by the DNA containing the error or ambiguity. For example, in the sequences of the present invention, ambiguities
in the sequence of SEQ ID NO: 131 were resolved. The amino acid sequence of the protein encoded by a particular clone
can also be determined by expression of the clone in a suitable host cell, collecting the protein, and determining its
sequence.

For each amino acid sequence, Applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing. Some of the amino acid sequences may contain "Xaa" designators. These "Xaa" designators indicate either (1) a residue which cannot be identified because of nucleotide sequence ambiguity or (2) a stop codon in the determined sequence where Applicants believe one should not exist (if the sequence were determined more accurately).

Cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377) of the present invention in the vector pED6dpc2, are maintained in permanent deposit by the inventors at Genset, S.A., 24 Rue Royale, 75008 Paris, France.

Pools of cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377), from which cells containing a particular polynucleotide are obtainable, were deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209 or the European Collection of Cell Cultures, Vaccine Research and Production Laboratory, Public Health Laboratory Service, Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire SP4 OJG, United Kingdom. Each extended cDNA clone has been transfected into separate bacterial cells (E-

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coli) for this composite deposit. Table VI lists the deposit numbers of the clones containing the extended cDNAs of the present invention. Table VII provides the internal designation number assigned to each SEQ ID NO and indicates whether the sequence is a nucleic acid sequence or a protein sequence.

Each extended cDNA can be removed from the pED6dpc2 vector in which it was deposited by performing a 5 Notl, Pstl double digestion to produce the appropriate fragment for each clone. The proteins encoded by the extended cDNAs may also be expressed from the promoter in pED6dpc2.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The design 10 of the oligonucleotide probe should preferably follow these parameters:

- (a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;
- (b) Preferably, the probe is designed to have a T_m of approx. 80°C (assuming 2 degrees for each A or T and 4 degrees for each G or C). However, probes having melting temperatures between 40 °C and 80 °C may also be used provided that specificity is not lost.

The oligonucleotide should preferably be labeled with (-[32P]ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can aiso be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantified by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4X10⁶ dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 ug/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing 25 ampicillin at 100 μg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 30 175.3 g NaC1/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 pg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1X10⁶ dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to

1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

The plasmid DNA obtained using these procedures may then be manipulated using standard cloning techniques familiar to those skilled in the art. Alternatively, a PCR can be done with primers designed at both ends of the extended cDNA insertion. For example, a PCR reaction may be conducted using a primer having the sequence GGCCATACACTTGAGTGAC (SEQ ID NO:38) and a primer having the sequence ATATAGACAAACGCACACC (SEQ. ID. NO:39). The PCR product which corresponds to the extended cDNA can then be manipulated using standard cloning 10 techniques familiar to those skilled in the art.

In addition to PCR based methods for obtaining extended cDNAs, traditional hybridization based methods may also be employed. These methods may also be used to obtain the genomic DNAs which encode the mRNAs from which the 5' ESTs were derived, mRNAs corresponding to the extended cDNAs, or nucleic acids which are homologous to extended cDNAs or 5' ESTs. Example 29 below provides an example of such methods.

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EXAMPLE 29

Methods for Obtaining Extended cDNAs or Nucleic Acids Homologous to Extended cDNAs or 5' ESTs

A full length cDNA library can be made using the strategies described in Examples 13, 14, 15, and 16 above by replacing the random nonamer used in Example 14 with an oligo-dT primer. For instance, the oligonucleotide of SEQ ID 20 NO:14 may be used.

Alternatively, a cDNA library or genomic DNA library may be obtained from a commercial source or made using techniques familiar to those skilled in the art. The library includes cDNAs which are derived from the mRNA corresponding to a 5' EST or which have homology to an extended cDNA or 5' EST. The cDNA library or genomic DNA library is hybridized to a detectable probe comprising at least 10 consecutive nucleotides from the 5' EST or extended 25 cDNA using conventional techniques. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises at least 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 30 nucleotides from the 5' EST or extended cDNA. In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

Techniques for identifying cDNA clones in a cDNA library which hybridize to a given probe sequence are disclosed in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold Spring Harbor Laboratory Press, 1989. The same techniques may be used to isolate genomic DNAs.

Briefly, cDNA or genomic DNA clones which hybridize to the detectable probe are identified and isolated for further manipulation as follows. A probe comprising at least 10 consecutive nucleotides from the 5' EST or extended cDNA is labeled with a detectable label such as a radioisotope or a fluorescent molecule. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises more than 30 nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

Techniques for labeling the probe are well known and include phosphorylation with polynucleotide kinase, nick translation, in vitro transcription, and non-radioactive techniques. The cDNAs or genomic DNAs in the library are transferred to a nitrocellulose or nylon filter and denatured. After incubation of the filter with a blocking solution, the filter is contacted with the labeled probe and incubated for a sufficient amount of time for the probe to hybridize to cDNAs or genomic DNAs containing a sequence capable of hybridizing to the probe.

By varying the stringency of the hybridization conditions used to identify extended cDNAs or genomic DNAs which hybridize to the detectable probe, extended cDNAS having different levels of homology to the probe can be identified and isolated. To identify extended cDNAs or genomic DNAs having a high degree of homology to the probe sequence, the melting temperature of the probe may be calculated using the following formulas:

For probes between 14 and 70 nucleotides in length the melting temperature (Tm) is calculated using the formula: Tm = 81.5 + 16.6(log [Na +]) + 0.41(fraction G + C)-(600/N) where N is the length of the probe.

If the hybridization is carried out in a solution containing formamide, the melting temperature may be calculated using the equation Tm = 81.5 + 16.6(log (Na +)) + 0.41(fraction G + C)-(0.63% formamide)-(600/N) where N is the length of the probe.

Prehybridization may be carried out in 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100µg denatured fragmented salmon sperm DNA or 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100µg denatured fragmented salmon sperm DNA, 50% formamide. The formulas for SSC and Denhardt's solutions are listed in Sambrook et al., supra.

Hybridization is conducted by adding the detectable probe to the prehybridization solutions listed above. Where
the probe comprises double stranded DNA, it is denatured before addition to the hybridization solution. The filter is
contacted with the hybridization solution for a sufficient period of time to allow the probe to hybridize to extended
cDNAs or genomic DNAs containing sequences complementary thereto or homologous thereto. For probes over 200
nucleotides in length, the hybridization may be carried out at 15-25°C below the Tm. For shorter probes, such as
oligonucleotide probes, the hybridization may be conducted at 15-25°C below the Tm. Preferably, for hybridizations in

6X SSC, the hybridization is conducted at approximately 68°C. Preferably, for hybridizations in 50% formamide
containing solutions, the hybridization is conducted at approximately 42°C.

All of the foregoing hybridizations would be considered to be under "stringent" conditions. Following hybridization, the filter is washed in 2X SSC, 0.1% SDS at room temperature for 15 minutes. The filter is then washed

with 0.1X SSC, 0.5% SDS at room temperature for 30 minutes to 1 hour. Thereafter, the solution is washed at the hybridization temperature in 0.1X SSC, 0.5% SDS. A final wash is conducted in 0.1X SSC at room temperature.

Extended cDNAs, nucleic acids homologous to extended cDNAs or 5' ESTs, or genomic DNAs which have hybridized to the probe are identified by autoradiography or other conventional techniques.

The above procedure may be modified to identify extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs having decreasing levels of homology to the probe sequence. For example, to obtain extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs of decreasing homology to the detectable probe, less stringent conditions may be used. For example, the hybridization temperature may be decreased in increments of 5°C from 68°C to 42°C in a hybridization buffer having a Na+ concentration of approximately 1M. Following 10 hybridization, the filter may be washed with 2X SSC, 0.5% SDS at the temperature of hybridization. These conditions are considered to be "moderate" conditions above 50°C and "low" conditions below 50°C.

Alternatively, the hybridization may be carried out in buffers, such as 6X SSC, containing formamide at a temperature of 42°C. In this case, the concentration of formamide in the hybridization buffer may be reduced in 5% increments from 50% to 0% to identify clones having decreasing levels of homology to the probe. Following 15 hybridization, the filter may be washed with 6X SSC, 0.5% SDS at 50°C. These conditions are considered to be "moderate" conditions above 25% formamide and "low" conditions below 25% formamide.

Extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs which have hybridized to the probe are identified by autoradiography.

If it is desired to obtain nucleic acids homologous to extended cDNAs, such as allelic variants thereof or nucleic 20 acids encoding proteins related to the proteins encoded by the extended cDNAs, the level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may readily be determined. To determine the level of homology between the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived, the nucleotide seguences of the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived are compared. For example, using the above methods, nucleic acids having at least 95% nucleic acid 25 homology to the extended cDNA or 5'EST from which the probe was derived may be obtained and identified. Similarly, by using progressively less stringent hybridization conditions one can obtain and identify nucleic acids having at least 90%, at least 85%, at least 80% or at least 75% homology to the extended cDNA or 5'EST from which the probe was derived. The level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may be further determined using BLAST2N; parameters may be adapted depending on the sequence length and degree of homology studied. In such comparisons, the default parameters or the parameters listed in Tables II and III may be used.

To determine whether a clone encodes a protein having a given amount of homology to the protein encoded by the extended cDNA or 5' EST, the amino acid sequence encoded by the extended cDNA or 5' EST is compared to the amino acid sequence encoded by the hybridizing nucleic acid. Homology is determined to exist when an amino acid sequence in the extended cDNA or 5' EST is closely related to an amino acid sequence in the hybridizing nucleic acid. A

sequence is closely related when it is identical to that of the extended cDNA or 5' EST or when it contains one or more amino acid substitutions therein in which amino acids having similar characteristics have been substituted for one another. Using the above methods, one can obtain nucleic acids encoding proteins having at least 95%, at least 90%, at least 85%, at least 80% or at least 75% homology to the proteins encoded by the extended cDNA or 5'EST from which the probe was derived. Using the above methods and algorithms such as FASTA with parameters depending on the sequence length and degree of homology studied the level of homology may be determined. In determining the level of homology using FASTA, the default parameters or the parameters listed in Tables II or III may be used.

Alternatively, extended cDNAs may be prepared by obtaining mRNA from the tissue, cell, or organism of interest using mRNA preparation procedures utilizing poly A selection procedures or other techniques known to those skilled in the art. A first primer capable of hybridizing to the poly A tail of the mRNA is hybridized to the mRNA and a reverse transcription reaction is performed to generate a first cDNA strand.

The first cDNA strand is hybridized to a second primer containing at least 10 consecutive nucleotides of the sequences of the 5' EST for which an extended cDNA is desired. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the sequences of the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the sequences of the 5' EST. In some embodiments, the primer comprises more than 30 nucleotides from the sequences of the 5' EST. If it is desired to obtain extended cDNAs containing the full protein coding sequence, including the authentic translation initiation site, the second primer used contains sequences located upstream of the translation initiation site. The second primer is extended to generate a second cDNA strand complementary to the first cDNA strand. Alternatively, RTPCR may be performed as described above using primers from both ends of the cDNA to be obtained.

Extended cDNAs containing 5' fragments of the mRNA may be prepared by contacting an mRNA comprising the sequence of the 5' EST for which an extended cDNA is desired with a primer comprising at least 10 consecutive nucleotides of the sequences complementary to the 5' EST, hybridizing the primer to the mRNAs, and reverse transcribing the hybridized primer to make a first cDNA strand from the mRNAs. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the 5' EST.

Thereafter, a second cDNA strand complementary to the first cDNA strand is synthesized. The second cDNA strand may be made by hybridizing a primer complementary to sequences in the first cDNA strand to the first cDNA strand and extending the primer to generate the second cDNA strand.

The double stranded extended cDNAs made using the methods described above are isolated and cloned. The extended cDNAs may be cloned into vectors such as plasmids or viral vectors capable of replicating in an appropriate host cell. For example, the host cell may be a bacterial, mammalian, avian, or insect cell.

Techniques for isolating mRNA, reverse transcribing a primer hybridized to mRNA to generate a first cDNA strand, extending a primer to make a second cDNA strand complementary to the first cDNA strand, isolating the double

stranded cDNA and cloning the double stranded cDNA are well known to those skilled in the art and are described in Current Protocols in Molecular Biology, John Wiley 503 Sons, Inc. 1997 and Sambrook et al. Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989.

Alternatively, kits for obtaining full length cDNAs, such as the GeneTrapper (Cat. No. 10356-020, Gibco, BRL),

may be used for obtaining full length cDNAs or extended cDNAs. In this approach, full length or extended cDNAs are
prepared from mRNA and cloned into double stranded phagemids. The cDNA library in the double stranded phagemids is
then rendered single stranded by treatment with an endonuclease, such as the Gene II product of the phage F1, and
Exonuclease III as described in the manual accompanying the GeneTrapper kit. A biotinylated oligonucleotide comprising
the sequence of a 5' EST, or a fragment containing at least 10 nucleotides thereof, is hybridized to the single stranded
phagemids. Preferably, the fragment comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More
preferably, the fragment comprises 20-30 consecutive nucleotides from the 5' EST. In some procedures, the fragment
may comprise more than 30 consecutive nucleotides from the 5' EST. For example, the fragment may comprises at least
40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST.

Hybrids between the biotinylated oligonucleotide and phagemids having inserts containing the 5' EST sequence
are isolated by incubating the hybrids with streptavidin coated paramagnetic beads and retrieving the beads with a
magnet. Thereafter, the resulting phagemids containing the 5' EST sequence are released from the beads and converted
into double stranded DNA using a primer specific for the 5' EST sequence. The resulting double stranded DNA is
transformed into bacteria. Extended cDNAs containing the 5' EST sequence are identified by colony PCR or colony
hybridization.

A plurality of extended cDNAs containing full length protein coding sequences or sequences encoding only the mature protein remaining after the signal peptide is cleaved may be provided as cDNA libraries for subsequent evaluation of the encoded proteins or use in diagnostic assays as described below.

IV. Expression of Proteins Encoded by Extended cDNAs Isolated Using 5' ESTs

Extended cDNAs containing the full protein coding sequences of their corresponding mRNAs or portions
thereof, such as cDNAs encoding the mature protein, may be used to express the secreted proteins or portions thereof which they encode as described in Example 30 below. If desired, the extended cDNAs may contain the sequences encoding the signal peptide to facilitate secretion of the expressed protein. It will be appreciated that a plurality of extended cDNAs containing the full protein coding sequences or portions thereof may be simultaneously cloned into expression vectors to create an expression library for analysis of the encoded proteins as described below.

30 EXAMPLE 30

Expression of the Proteins Encoded by Extended cDNAs or Portions Thereof

To express the proteins encoded by the extended cDNAs or portions thereof, nucleic acids containing the coding sequence for the proteins or portions thereof to be expressed are obtained as described in Examples 27-29 and cloned into a suitable expression vector. If desired, the nucleic acids may contain the sequences encoding the signal

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peptide to facilitate secretion of the expressed protein. For example, the nucleic acid may comprise the sequence of one of SEQ ID NOs: 40-140 and 242-377 listed in Table IV and in the accompanying sequence listing. Alternatively, the nucleic acid may comprise those nucleotides which make up the full coding sequence of one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

It will be appreciated that should the extent of the full coding sequence (i.e. the sequence encoding the signal peptide and the mature protein resulting from cleavage of the signal peptide) differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the full coding sequences in the sequences of SEQ ID NOs. 40-140 and 242-377. 10 For example, the sequence of SEQ ID NO: 115 represents an alternatively spliced transcript of a previously identified mRNA... Accordingly, the scope of any claims herein relating to nucleic acids containing the full coding sequence of one of SEQ ID NOs. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the full coding sequences listed in Table IV Similarly, should the extent of the full length polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides 15 comprising the amino acid sequence of the full length polypeptides is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V.

Alternatively, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the mature protein (i.e. the protein created by cleaving the signal peptide off) encoded by one of the sequences of SEO ID NOs: 40-140 and 242-377 as defined in Table IV above.

20 It will be appreciated that should the extent of the sequence encoding the mature protein differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, posttranslational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the mature protein in the sequences of SEO ID NOs. 40-140 and 242-377. Accordingly, the scope of any claims herein relating to nucleic acids 25 containing the sequence encoding the mature protein encoded by one of SEQ ID Nos. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table IV. Thus, claims relating to nucleic acids containing the sequence encoding the mature protein encompass equivalents to the sequences listed in Table IV, such as sequences encoding biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in 30 addition to cleavage of the signal peptide. Similarly, should the extent of the mature polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a mature protein included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V. Thus. claims relating to polypeptides comprising the sequence of the mature protein encompass equivalents to the sequences

listed in Table IV, such as biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in addition to cleavage of the signal peptide. It will also be appreciated that should the biologically active form of the polypeptides included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 or the nucleic acids encoding the biologically active form of the polypeptides differ from those identified as the mature polypeptide in Table V or the nucleotides encoding the mature polypeptide in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the amino acids in the biologically active form of the polypeptides and the nucleic acids encoding the biologically active form of the polypeptides. In such instances, the claims relating to polypetides comprising the mature protein included in one of SEQ ID NOs. 141-241 and 378-513 or nucleic acids comprising the nucleotides of one of SEQ ID NOs. 40-140 and 242-377 encoding the mature protein shall not be construed to exclude any readily identifiable variations from the sequences listed in Table IV and Table V.

In some embodiments, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the signal peptide encoded by one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

It will be appreciated that should the extent of the sequence encoding the signal peptide differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the signal peptide in the sequences of SEQ ID Nos. 40-140 and 242-377. Accordingly, the scope of any claims herein relating to nucleic acids containing the sequence encoding the signal peptide encoded by one of SEQ ID Nos. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table IV. Similarly, should the extent of the signal peptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a signal peptide included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table V.

Alternatively, the nucleic acid may encode a polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In some embodiments, the nucleic acid may encode a polypeptide comprising at least 15 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 60, at least 75, at least 100 or more than 100 consecutive amino acids of one of the sequences of SEQ ID Nos: 141-241 and 378-513.

The nucleic acids inserted into the expression vectors may also contain sequences upstream of the sequences encoding the signal peptide, such as sequences which regulate expression levels or sequences which confer tissue specific expression.

The nucleic acid encoding the protein or polypeptide to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The expression vector may be any of the mammalian, yeast, insect or bacterial expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon context and codon pairing of the sequence may be optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, et al., U.S. Patent No. 5,082,767.

The following is provided as one exemplary method to express the proteins encoded by the extended cDNAs corresponding to the 5' ESTs or the nucleic acids described above. First, the methionine initiation codon for the gene and the poly A signal of the gene are identified. If the nucleic acid encoding the polypeptide to be expressed lacks a methionine to serve as the initiation site, an initiating methionine can be introduced next to the first codon of the nucleic acid using conventional techniques. Similarly, if the extended cDNA lacks a poly A signal, this sequence can be added to the construct by, for example, splicing out the Poly A signal from pSG5 (Stratagene) using Bgll and Sall restriction endonuclease enzymes and incorporating it into the mammalian expression vector pXT1 (Stratagene). pXT1 contains the LTRs and a portion of the gag gene from Moloney Murine Leukemia Virus. The position of the LTRs in the construct allow efficient stable transfection. The vector includes the Herpes Simplex Thymidine Kinase promoter and the selectable neomycin gene. The extended cDNA or portion thereof encoding the polypeptide to be expressed is obtained by PCR from the bacterial vector using oligonucleotide primers complementary to the extended cDNA or portion thereof and containing restriction endonuclease sequences for Pst I incorporated into the 5'primer and Bglll at the 5' end of the corresponding cDNA 3' primer, taking care to ensure that the extended cDNA is positioned in frame with the poly A signal. The purified fragment obtained from the resulting PCR reaction is digested with Pstl, blunt ended with an exonuclease, digested with Bglll, purified and ligated to pXT1, now containing a poly A signal and digested with Bglll.

The ligated product is transfected into mouse NIH 3T3 cells using Lipofectin (Life Technologies, Inc., Grand Island, New York) under conditions outlined in the product specification. Positive transfectants are selected after growing the transfected cells in 600ug/ml G418 (Sigma, St. Louis, Missouri). Preferably the expressed protein is released into the culture medium, thereby facilitating purification.

Alternatively, the extended cDNAs may be cloned into pED6dpc2 as described above. The resulting pED6dpc2 constructs may be transfected into a suitable host cell, such as COS 1 cells. Methotrexate resistant cells are selected and expanded. Preferably, the protein expressed from the extended cDNA is released into the culture medium thereby facilitating purification.

Proteins in the culture medium are separated by gel electrophoresis. If desired, the proteins may be ammonium sulfate precipitated or separated based on size or charge prior to electrophoresis.

As a control, the expression vector lacking a cDNA insert is introduced into host cells or organisms and the proteins in the medium are harvested. The secreted proteins present in the medium are detected using techniques such as Coomassie or silver staining or using antibodies against the protein encoded by the extended cDNA. Coomassie and silver staining techniques are familiar to those skilled in the art.

Antibodies capable of specifically recognizing the protein of interest may be generated using synthetic 15-mer peptides having a sequence encoded by the appropriate 5' EST, extended cDNA, or portion thereof. The synthetic peptides are injected into mice to generate antibody to the polypeptide encoded by the 5' EST, extended cDNA, or portion thereof.

Secreted proteins from the host cells or organisms containing an expression vector which contains the extended cDNA derived from a 5' EST or a portion thereof are compared to those from the control cells or organism. The presence of a band in the medium from the cells containing the expression vector which is absent in the medium from the control cells indicates that the extended cDNA encodes a secreted protein. Generally, the band corresponding to the protein encoded by the extended cDNA will have a mobility near that expected based on the number of amino acids in the open reading frame of the extended cDNA. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

Alternatively, if the protein expressed from the above expression vectors does not contain sequences directing its secretion, the proteins expressed from host cells containing an expression vector containing an insert encoding a secreted protein or portion thereof can be compared to the proteins expressed in host cells containing the expression vector without an insert. The presence of a band in samples from cells containing the expression vector with an insert which is absent in samples from cells containing the expression vector without an insert indicates that the desired protein or portion thereof is being expressed. Generally, the band will have the mobility expected for the secreted protein or portion thereof. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

The protein encoded by the extended cDNA may be purified using standard immunochromatography techniques. In such procedures, a solution containing the secreted protein, such as the culture medium or a cell extract, is applied to a column having antibodies against the secreted protein attached to the chromatography matrix. The secreted protein is allowed to bind the immunochromatography column. Thereafter, the column is washed to remove non-specifically bound proteins. The specifically bound secreted protein is then released from the column and recovered using standard techniques.

If antibody production is not possible, the extended cDNA sequence or portion thereof may be incorporated into expression vectors designed for use in purification schemes employing chimeric polypeptides. In such strategies the coding sequence of the extended cDNA or portion thereof is inserted in frame with the gene encoding the other half of

the chimera. The other half of the chimera may be β -globin or a nickel binding polypeptide encoding sequence. A chromatography matrix having antibody to β -globin or nickel attached thereto is then used to purify the chimeric protein. Protease cleavage sites may be engineered between the β -globin gene or the nickel binding polypeptide and the extended cDNA or portion thereof. Thus, the two polypeptides of the chimera may be separated from one another by protease digestion.

One useful expression vector for generating β-globin chimerics is pSG5 (Stratagene), which encodes rabbit β-globin. Intron II of the rabbit β-globin gene facilitates splicing of the expressed transcript, and the polyadenylation signal incorporated into the construct increases the level of expression. These techniques as described are well known to those skilled in the art of molecular biology. Standard methods are published in methods texts such as Davis et al.,

10 (Basic Methods in Molecular Biology, L.G. Davis, M.D. Dibner, and J.F. Battey, ed., Elsevier Press, NY, 1986) and many of the methods are available from Stratagene, Life Technologies, Inc., or Promega. Polypeptide may additionally be produced from the construct using in vitro translation systems such as the In vitro ExpressTM Translation Kit (Stratagene).

Following expression and purification of the secreted proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof, the purified proteins may be tested for the ability to bind to the surface of various cell types as described in Example 31 below. It will be appreciated that a plurality of proteins expressed from these cDNAs may be included in a panel of proteins to be simultaneously evaluated for the activities specifically described below, as well as other biological roles for which assays for determining activity are available.

EXAMPLE 31

20 <u>Analysis of Secreted Proteins to Determine Whether they Bind to the Cell Surface</u>

The proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof are cloned into expression vectors such as those described in Example 30. The proteins are purified by size, charge, immunochromatography or other techniques familiar to those skilled in the art. Following purification, the proteins are labeled using techniques known to those skilled in the art. The labeled proteins are incubated with cells or cell lines derived from a variety of organs or tissues to allow the proteins to bind to any receptor present on the cell surface. Following the incubation, the cells are washed to remove non-specifically bound protein. The labeled proteins are detected by autoradiography. Alternatively, unlabeled proteins may be incubated with the cells and detected with antibodies having a detectable label, such as a fluorescent molecule, attached thereto.

Specificity of cell surface binding may be analyzed by conducting a competition analysis in which various

amounts of unlabeled protein are incubated along with the labeled protein. The amount of labeled protein bound to the
cell surface decreases as the amount of competitive unlabeled protein increases. As a control, various amounts of an
unlabeled protein unrelated to the labeled protein is included in some binding reactions. The amount of labeled protein
bound to the cell surface does not decrease in binding reactions containing increasing amounts of unrelated unlabeled
protein, indicating that the protein encoded by the cDNA binds specifically to the cell surface.

As discussed above, secreted proteins have been shown to have a number of important physiological effects and, consequently, represent a valuable therapeutic resource. The secreted proteins encoded by the extended cDNAs or portions thereof made according to Examples 27-29 may be evaluated to determine their physiological activities as described below.

5 EXAMPLE 32

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Cytokine, Cell Proliferation or Cell Differentiation Activity

As discussed above, secreted proteins may act as cytokines or may affect cellular proliferation or differentiation. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B5, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7c and CMK. The proteins encoded by the above extended cDNAs or portions thereof may be evaluated for their ability to regulate T cell or thymocyte proliferation in assays such as those described above or in the following references: Current Protocols in Immunology, Ed. by J.E. Coligan et al., Greene Publishing Associates and Wiley-Interscience; Takai et al. J. Immunol. 137:3494-3500, 1986. Bertagnolli et al. J. Immunol. 145:1706-1712, 1990. Bertagnolli et al., Cellular Immunology 133:327-341, 1991. Bertagnolli, et al. J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152:1756-1761, 1994.

In addition, numerous assays for cytokine production and/or the proliferation of spleen cells, lymph node cells
and thymocytes are known. These include the techniques disclosed in Current Protocols in Immunology. J.E. Coligan
et al. Eds., Vol 1 pp. 3.12.1-3.12.14 John Wiley and Sons, Toronto. 1994; and Schreiber, R.D. Current Protocols in
Immunology., supra Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be assayed for the ability to regulate the proliferation and differentiation of hematopoietic or lymphopoietic cells. Many assays for such activity are familiar to those skilled in the art, including the assays in the following references: Bottomly, K., Davis, L.S. and Lipsky, P.E., Measurement of Human and Murine Interleukin 2 and Interleukin 4, Current Protocols in Immunology., J.E. Coligan et al. Eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 36:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Nordan, R., Measurement of Mouse and Human Interleukin 6 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Bennett, F., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Human Interleukin 11 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Mouse and Human Interleukin 9 Current Protocols in Immunology. J.E. Coligan et al., Eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

The proteins encoded by the cDNAs may also be assayed for their ability to regulate T-cell responses to antigens. Many assays for such activity are familiar to those skilled in the art, including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function), Chapter 6 (Cytokines and Their Cellular Receptors) and Chapter 7, (Immunologic Studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Those proteins which exhibit cytokine, cell proliferation, or cell differentiation activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which induction of cell proliferation or differentiation is

10 beneficial. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 33

Assaying the Proteins Expressed from Extended cDNAs or Portions

Thereof for Activity as Immune System Regulators

The proteins encoded by the cDNAs may also be evaluated for their effects as immune regulators. For example, the proteins may be evaluated for their activity to influence thymocyte or splenocyte cytotoxicity. Numerous assays for such activity are familiar to those skilled in the art including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function 3.1-3.19) and Chapter 7 (Immunologic studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds, Greene Publishing Associates and Wiley-Interscience; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

The proteins encoded by the cDNAs may also be evaluated for their effects on T-cell dependent immunoglobulin responses and isotype switching. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Maliszewski, J. Immunol. 144:3028-3033, 1990; Mond, J.J. and Brunswick, M Assays for B Cell Function: *In vitro* Antibody Production, Vol 1 pp. 3.8.1-3.8.16 in Current Protocols in Immunology. J.E. Coligan et al Eds., John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be evaluated for their effect on immune effector cells, including their effect on Th1 cells and cytotoxic lymphocytes. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte

Function 3.1-3.19) and Chapter 7 (Immunologic Studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds., Greene Publishing Associates and Wiley-Interscience; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

The proteins encoded by the cDNAs may also be evaluated for their effect on dendritic cell mediated activation of naive T-cells. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

The proteins ercoded by the cDNAs may also be evaluated for their influence on the lifetime of lymphocytes.

Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Those proteins which exhibit activity as immune system regulators activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of immune activity is beneficial. For example, the protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis,

myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to regulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T-cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. 10 Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte 15 antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 20 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an 25 immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed 30 using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4lg fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models

of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead 10 to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/pr/pr mice or NZB hybrid mice, murine autoimmuno collagen arthritis, diabetes mellitus in OD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory 20 form of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to T cells 25 in vivo, thereby activating the T cells.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be 30 transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acids encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β2 macroglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class II or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain,can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 34

<u>Assaying the Proteins Expressed from Extended cDNAs</u> or Portions Thereof for Hematopoiesis Regulating Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their hematopoiesis regulating activity. For example, the effect of the proteins on embryonic stem cell differentiation may be evaluated. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their influence on the lifetime of stem cells and stem cell differentiation. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Freshney, M.G. Methylcellulose Colony Forming Assays, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; McNiece, I.K. and Briddell, R.A. Primitive Hematopoietic Colony Forming Cells with High Proliferative Potential, in Culture of Hematopoietic Cells. R.I. 30 Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Ploemacher, R.E. Cobblestone Area Forming Cell Assay, In Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Spooncer, E., Dexter, M. and Allen, T. Long Term Bone Marrow Cultures in the Presence of Stromal Cells, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds.

pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; and Sutherland, H.J. Long Term Culture Initiating Cell Assay, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Those proteins which exhibit hematopoiesis regulatory activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of hematopoeisis is beneficial. For example, a protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid 10 cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelosuppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem 15 cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantion, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or 20 genetically manipulated for gene therapy. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 35

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Tissue Growth

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effect on tissue growth. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in International Patent Publication No. W095/16035, International Patent Publication No. W095/05846 and International Patent Publication No. W091/07491.

Assays for wound healing activity include, without limitation, those described in: Winter, <u>Epidermal Wound</u>

30 <u>Healing</u>, pps. 71-112 (Maibach, H1 and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Those proteins which are involved in the regulation of tissue growth may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of tissue growth is beneficial. For example, a protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or

nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to 20 tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate 25 growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of 30 nerve and brain tissue, i.e., for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium) muscle

(smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to generate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokinc damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

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EXAMPLE 36

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Reproductive Hormones or Cell Movement

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their ability to regulate reproductive hormones, such as follicle stimulating hormone. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986. Chapter 6.12 (Measurement of Alpha and Beta Chemokines) Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Intersciece; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al. Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153:1762-1768, 1994.

Those proteins which exhibit activity as reproductive hormones or regulators of cell movement may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of reproductive hormones or cell movement are beneficial. For example, a protein of the present invention may also exhibit activin- or inhibin-related

activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of folic stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals.

Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-B group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 36A

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Assaying the Proteins Expressed from Extended cDNAs or

Portions Thereof for Chemotactic/Chemokinetic Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for chemotactic/chemokinetic activity. For example, a protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, cosinophils, epithelial and/or endothelial cells. Chemotactic and chmokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhension of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12,

Measurement of alpha and beta Chemokincs 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Mueller et al Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol, 153:1762-1768, 1994.

EXAMPLE 37

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Assaying the Proteins Expressed from Extended cDNAs or

Portions Thereof for Regulation of Blood Clotting

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effects on blood clotting. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res.

45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Those proteins which are involved in the regulation of blood clotting may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of blood clotting is beneficial. For example, a protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulations disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke). Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 38

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Involvement in Receptor/Ligand Interactions

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for their involvement in receptor/ligand interactions. Numerous assays for such involvement are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 7.28 (Measurement of Cellular Adhesion under Static Conditions 7.28.1-7.28.22) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160, 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995; Gyuris et al., Cell 75:791-803, 1993.

For example, the proteins of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion

molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune respones). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

EXAMPLE 38A

Assaying the Proteins Expressed from Extended cDNAs or Portions

Thereof for Anti-Inflammatory Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusioninury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

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EXAMPLE 38B

Assaying the Proteins Expressed from Extended cDNAs or

Portions Thereof for Tumor Inhibition Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for tumor inhibition activity. In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, climinating or inhibiting factors, agents or cell types which promote tumor growth.

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or

circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or climination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

EXAMPLE 39

Identification of Proteins which Interact with Polypeptides Encoded by Extended cDNAs

Proteins which interact with the polypeptides encoded by extended cDNAs or portions thereof, such as

receptor proteins, may be identified using two hybrid systems such as the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech). As described in the manual accompanying the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech), the extended cDNAs or portions thereof, are inserted into an expression vector such that they are in frame with DNA encoding the DNA binding domain of the yeast transcriptional activator GAL4. cDNAs in a cDNA library which encode proteins which might interact with the polypeptides encoded by the extended cDNAs or portions thereof are inserted into a second expression vector such that they are in frame with DNA encoding the activation domain of GAL4. The two expression plasmids are transformed into yeast and the yeast are plated on selection medium which selects for expression of selectable markers on each of the expression vectors as well as GAL4 dependent expression of the HIS3 gene. Transformants capable of growing on medium lacking histidine are screened for GAL4 dependent lacZ expression. Those cells which are positive in both the histidine selection and the lacZ assay contain plasmids encoding proteins which interact with the polypeptide encoded by the extended cDNAs or portions thereof.

Alternatively, the system described in Lustig et al., Methods in Enzymology 283: 83-99 (1997) may be used for identifying molecules which interact with the polypeptides encoded by extended cDNAs. In such systems, in vitro transcription reactions are performed on a pool of vectors containing extended cDNA inserts cloned downstream of a promoter which drives in vitro transcription. The resulting pools of mRNAs are introduced into Xenopus laevis oocytes.

30 The oocytes are then assayed for a desired activity.

Alternatively, the pooled *in vitro* transcription products produced as described above may be translated *in vitro*. The pooled *in vitro* translation products can be assayed for a desired activity or for interaction with a known polypeptide.

Proteins or other molecules interacting with polypeptides encoded by extended cDNAs can be found by a variety of additional techniques. In one method, affinity columns containing the polypeptide encoded by the extended cDNA or a portion thereof can be constructed. In some versions, of this method the affinity column contains chimeric proteins in which the protein encoded by the extended cDNA or a portion thereof is fused to glutathione S-transferase.

5 A mixture of cellular proteins or pool of expressed proteins as described above and is applied to the affinity column. Proteins interacting with the polypeptide attached to the column can then be isolated and analyzed on 2-D electrophoresis gel as described in Ramunsen et al. Electrophoresis, 18, 588-598 (1997). Alternatively, the proteins retained on the affinity column can be purified by electrophoresis based methods and sequenced. The same method can be used to isolate antibodies, to screen phage display products, or to screen phage display human antibodies.

Proteins interacting with polypeptides encoded by extended cDNAs or portions thereof can also be screened by using an Optical Biosensor as described in Edwards & Leatherbarrow, Analytical Biochemistry, 246, 1-6 (1997). The main advantage of the method is that it allows the determination of the association rate between the protein and other interacting molecules. Thus, it is possible to specifically select interacting molecules with a high or low association rate. Typically a target molecule is linked to the sensor surface (through a carboxymethl dextran matrix) and a sample of test 15 molecules is placed in contact with the target molecules. The binding of a test molecule to the target molecule causes a change in the refractive index and/ or thickness. This change is detected by the Biosensor provided it occurs in the evanescent field (which extend a few hundred manometers from the sensor surface). In these screening assays, the target molecule can be one of the polypeptides encoded by extended cDNAs or a portion thereof and the test sample can be a collection of proteins extracted from tissues or cells, a pool of expressed proteins, combinatorial peptide and/ or 20 chemical libraries, or phage displayed peptides. The tissues or cells from which the test proteins are extracted can originate from any species.

In other methods, a target protein is immobilized and the test population is a collection of unique polypeptides encoded by the extended cDNAs or portions thereof.

To study the interaction of the proteins encoded by the extended cDNAs or portions thereof with drugs, the 25 microdialysis coupled to HPLC method described by Wang et al., Chromatographia, 44, 205-208(1997) or the affinity capillary electrophoresis method described by Busch et al., J. Chromatogr. 777:311-328 (1997), the disclosures of which are incorporated herein by referenc can be used.

The system described in U.S. Patent No. 5,654,150 may also be used to identify molecules which interact with the polypeptides encoded by the extended cDNAs. In this system, pools of extended cDNAs are transcribed and 30 translated in vitro and the reaction products are assayed for interaction with a known polypeptide or antibody.

It will be appreciated by those skilled in the art that the proteins expressed from the extended cDNAs or portions may be assayed for numerous activities in addition to those specifically enumerated above. For example, the expressed proteins may be evaluated for applications involving control and regulation of inflammation, tumor

proliferation or metastasis, infection, or other clinical conditions. In addition, the proteins expressed from the extended cDNAs or portions thereof may be useful as nutritional agents or cosmetic agents.

The proteins expressed from the extended cDNAs or portions thereof may be used to generate antibodies capable of specifically binding to the expressed protein or fragments thereof as described in Example 40 below. The antibodies may capable of binding a full length protein encoded by one of the sequences of SEQ ID NOs. 40-140 and 242-377, or a signal peptide encoded by one of the sequences of SEQ ID Nos. 40-140 and 242-377, or a signal peptide encoded by one of the sequences of SEQ ID Nos. 40-140 and 242-377. Alternatively, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 10 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In some embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 15 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 25 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In further embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 40 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513.

EXAMPLE 40

Production of an Antibody to a Human Protein

Substantially pure protein or polypeptide is isolated from the transfected or transformed cells as described in Example 30. The concentration of protein in the final preparation is adjusted, for example, by concentration on an Amicon filter device, to the level of a few micrograms/ml. Monoclonal or polyclonal antibody to the protein can then be prepared as follows:

A. Monoclonal Antibody Production by Hybridoma Fusion

Monoclonal antibody to epitopes of any of the peptides identified and isolated as described can be prepared from murine hybridomas according to the classical method of Kohler, G. and Milstein, C., Nature 256:495 (1975) or derivative methods thereof. Briefly, a mouse is repetitively inoculated with a few micrograms of the selected protein or peptides derived therefrom over a period of a few weeks. The mouse is then sacrificed, and the antibody producing cells of the spleen isolated. The spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the culture is continued. Antibody producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as Elisa, as originally described by Engvall, E., Meth. Enzymol. 70:419 (1980), and derivative methods thereof. Selected positive clones can be expanded and their monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Davis, L. et al. Basic Methods in Molecular Biology Elsevier, New York. Section 21-2.

B. Polyclonal Antibody Production by Immunization

Polyclonal antiserum containing antibodies to heterogenous epitopes of a single protein can be prepared by immunizing suitable animals with the expressed protein or peptides derived therefrom described above, which can be unmodified or modified to enhance immunogenicity. Effective polyclonal antibody production is affected by many factors related both to the antigen and the host species. For example, small molecules tend to be less immunogenic than others and may require the use of carriers and adjuvant. Also, host animals vary in response to site of inoculations and dose, with both inadequate or excessive doses of antigen resulting in low titer antisera. Small doses (ng level) of antigen administered at multiple intradermal sites appears to be most reliable. An effective immunization protocol for rabbits can be found in Vaitukaitis, J. et al. J. Clin. Endocrinol. Metab. 33:988-991 (1971).

Booster injections can be given at regular intervals, and antiserum harvested when antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against known concentrations of the antigen, begins to fall. See, for example, Ouchterlony, O. et al., Chap. 19 in: Handbook of Experimental immunology D. Wier (ed) Blackwell (1973). Plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12 μ M). Affinity of the antisera for the antigen is determined by preparing competitive binding curves, as 15 described, for example, by Fisher, D., Chap. 42 in: Manual of Clinical Immunology, 2d Ed. (Rose and Friedman, Eds.) Amer. Soc. For Microbiol., Washington, D.C. (1980).

Antibody preparations prepared according to either protocol are useful in quantitative immunoassays which determine concentrations of antigen-bearing substances in biological samples; they are also used semi-quantitatively or qualitatively to identify the presence of antigen in a biological sample. The antibodies may also be used in therapeutic 20 compositions for killing cells expressing the protein or reducing the levels of the protein in the body.

V. Use of Extended cDNAs or Portions Thereof as Reagents

The extended cDNAs of the present invention may be used as reagents in isolation procedures, diagnostic assays, and forensic procedures. For example, sequences from the extended cDNAs (or genomic DNAs obtainable 25 therefrom) may be detectably labeled and used as probes to isolate other sequences capable of hybridizing to them. In addition, sequences from the extended cDNAs (or genomic DNAs obtainable therefrom) may be used to design PCR primers to be used in isolation, diagnostic, or forensic procedures.

EXAMPLE 41

Preparation of PCR Primers and Amplification of DNA

The extended cDNAs (or genomic DNAs obtainable therefrom) may be used to prepare PCR primers for a 30 variety of applications, including isolation procedures for cloning nucleic acids capable of hybridizing to such sequences, diagnostic techniques and forensic techniques. The PCR primers are at least 10 bases, and preferably at least 12, 15, or 17 bases in length. More preferably, the PCR primers are at least 20-30 bases in length. In some embodiments, the PCR primers may be more than 30 bases in length. It is preferred that the primer pairs have approximately the same G/C

ratio, so that melting temperatures are approximately the same. A variety of PCR techniques are familiar to those skilled in the art. For a review of PCR technology, see Molecular Cloning to Genetic Engineering White, B.A. Ed. in Methods in Molecular Biology 67: Humana Press, Totowa 1997. In each of these PCR procedures, PCR primers on either side of the nucleic acid sequences to be amplified are added to a suitably prepared nucleic acid sample along with 5 dNTPs and a thermostable polymerase such as Taq polymerase, Pfu polymerase, or Vent polymerase. The nucleic acid in the sample is denatured and the PCR primers are specifically hybridized to complementary nucleic acid sequences in the sample. The hybridized primers are extended. Thereafter, another cycle of denaturation, hybridization, and extension is initiated. The cycles are repeated multiple times to produce an amplified fragment containing the nucleic acid sequence between the primer sites.

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EXAMPLE 42

Use of Extended cDNAs as Probes

Probes derived from extended cDNAs or portions thereof (or genomic DNAs obtainable therefrom) may be labeled with detectable labels familiar to those skilled in the art, including radioisotopes and non-radioactive labels, to provide a detectable probe. The detectable probe may be single stranded or double stranded and may be made using 15 techniques known in the art, including in vitro transcription, nick translation, or kinase reactions. A nucleic acid sample containing a sequence capable of hybridizing to the labeled probe is contacted with the labeled probe. If the nucleic acid in the sample is double stranded, it may be denatured prior to contacting the probe. In some applications, the nucleic acid sample may be immobilized on a surface such as a nitrocellulose or nylon membrane. The nucleic acid sample may comprise nucleic acids obtained from a variety of sources, including genomic DNA, cDNA libraries, RNA, or tissue samples.

Procedures used to detect the presence of nucleic acids capable of hybridizing to the detectable probe include well known techniques such as Southern blotting, Northern blotting, dot blotting, colony hybridization, and plaque hybridization. In some applications, the nucleic acid capable of hybridizing to the labeled probe may be cloned into vectors such as expression vectors, sequencing vectors, or in vitro transcription vectors to facilitate the characterization 25 and expression of the hybridizing nucleic acids in the sample. For example, such techniques may be used to isolate and clone sequences in a genomic library or cDNA library which are capable of hybridizing to the detectable probe as described in Example 30 above.

PCR primers made as described in Example 41 above may be used in forensic analyses, such as the DNA fingerprinting techniques described in Examples 43-47 below. Such analyses may utilize detectable probes or primers 30 based on the sequences of the extended cDNAs isolated using the 5' ESTs (or genomic DNAs obtainable therefrom).

EXAMPLE 43

Forensic Matching by DNA Sequencing

In one exemplary method, DNA samples are isolated from forensic specimens of, for example, hair, semen, blood or skin cells by conventional methods. A panel of PCR primers based on a number of the extended cDNAs (or

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genomic DNAs obtainable therefrom), is then utilized in accordance with Example 41 to amplify DNA of approximately 100-200 bases in length from the forensic specimen. Corresponding sequences are obtained from a test subject. Each of these identification DNAs is then sequenced using standard techniques, and a simple database comparison determines the differences, if any, between the sequences from the subject and those from the sample. Statistically significant differences between the suspect's DNA sequences and those from the sample conclusively prove a lack of identity. This lack of identity can be proven, for example, with only one sequence. Identity, on the other hand, should be demonstrated with a large number of sequences, all matching. Preferably, a minimum of 50 statistically identical sequences of 100 bases in length are used to prove identity between the suspect and the sample.

EXAMPLE 44

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Positive Identification by DNA Sequencing

The technique outlined in the previous example may also be used on a larger scale to provide a unique fingerprint-type identification of any individual. In this technique, primers are prepared from a large number of sequences from Table IV and the appended sequence listing. Preferably, 20 to 50 different primers are used. These primers are used to obtain a corresponding number of PCR-generated DNA segments from the individual in question in accordance with Example 41. Each of these DNA segments is sequenced, using the methods set forth in Example 43. The database of sequences generated through this procedure uniquely identifies the individual from whom the sequences were obtained. The same panel of primers may then be used at any later time to absolutely correlate tissue or other biological specimen with that individual.

EXAMPLE 45

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Southern Blot Forensic Identification

The procedure of Example 44 is repeated to obtain a panel of at least 10 amplified sequences from an individual and a specimen. Preferably, the panel contains at least 50 amplified sequences. More preferably, the panel contains 100 amplified sequences. In some embodiments, the panel contains 200 amplified sequences. This PCR-generated DNA is then digested with one or a combination of, preferably, four base specific restriction enzymes. Such enzymes are commercially available and known to those of skill in the art. After digestion, the resultant gene fragments are size separated in multiple duplicate wells on an agarose gel and transferred to nitrocellulose using Southern blotting techniques well known to those with skill in the art. For a review of Southern blotting see Davis et al. (Basic Methods in Molecular Biology, 1986, Elsevier Press, pp 62-65).

A panel of probes based on the sequences of the extended cDNAs (or genomic DNAs obtainable therefrom), or fragments thereof of at least 10 bases, are radioactively or colorimetrically labeled using methods known in the art, such as nick translation or end labeling, and hybridized to the Southern blot using techniques known in the art (Davis et al., supra). Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30

nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

Preferably, at least 5 to 10 of these labeled probes are used, and more preferably at least about 20 or 30 are used to provide a unique pattern. The resultant bands appearing from the hybridization of a large sample of extended cDNAs (or genomic DNAs obtainable therefrom) will be a unique identifier. Since the restriction enzyme cleavage will be different for every individual, the band pattern on the Southern blot will also be unique. Increasing the number of extended cDNA probes will provide a statistically higher level of confidence in the identification since there will be an increased number of sets of bands used for identification.

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EXAMPLE 46

Dot Blot Identification Procedure

Another technique for identifying individuals using the extended cDNA sequences disclosed herein utilizes a dot blot hybridization technique.

Genomic DNA is isolated from nuclei of subject to be identified. Oligonucleotide probes of approximately 30 bp 15 in length are synthesized that correspond to at least 10, preferably 50 sequences from the extended cDNAs or genomic DNAs obtainable therefrom. The probes are used to hybridize to the genomic DNA through conditions known to those in the art. The oligonucleotides are end labeled with P³² using polynucleotide kinase (Pharmacia). Dot Blots are created by spotting the genomic DNA onto nitrocellulose or the like using a vacuum dot blot manifold (BioRad, Richmond California). The nitrocellulose filter containing the genomic sequences is baked or UV linked to the filter, prehybridized and 20 hybridized with labeled probe using techniques known in the art (Davis et al. supra). The 32P labeled DNA fragments are sequentially hybridized with successively stringent conditions to detect minimal differences between the 30 bp sequence and the DNA. Tetramethylammonium chloride is useful for identifying clones containing small numbers of nucleotide mismatches (Wood et al., Proc. Natl. Acad. Sci. USA 82(6):1585-1588 (1985)). A unique pattern of dots distinguishes one individual from another individual.

Extended cDNAs or oligonucleotides containing at least 10 consecutive bases from these sequences can be used as probes in the following alternative fingerprinting technique. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30 nucleotides from the extended cDNA (or genomic 30 DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

Preferably, a plurality of probes having sequences from different genes are used in the alternative fingerprinting technique. Example 47 below provides a representative alternative fingerprinting procedure in which the probes are derived from extended cDNAs.

EXAMPLE 47

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Alternative "Fingerprint" Identification Technique

20-mer oligonucleotides are prepared from a large number, e.g. 50, 100, or 200, of extended cDNA sequences (or genomic DNAs obtainable therefrom) using commercially available oligonucleotide services such as Genset, Paris, France. Cell samples from the test subject are processed for DNA using techniques well known to those with skill in the art. The nucleic acid is digested with restriction enzymes such as EcoRI and Xbal. Following digestion, samples are applied to wells for electrophoresis. The procedure, as known in the art, may be modified to accommodate polyacrylamide electrophoresis, however in this example, samples containing 5 ug of DNA are loaded into wells and separated on 0.8% agarose gels. The gels are transferred onto nitrocellulose using standard Southern blotting techniques.

10 ng of each of the oligonucleotides are pooled and end-labeled with P³². The nitrocellulose is prehybridized with blocking solution and hybridized with the labeled probes. Following hybridization and washing, the nitrocellulose filter is exposed to X-Omat AR X-ray film. The resulting hybridization pattern will be unique for each individual.

It is additionally contemplated within this example that the number of probe sequences used can be varied for additional accuracy or clarity.

The antibodies generated in Examples 30 and 40 above may be used to identify the tissue type or cell species from which a sample is derived as described above.

EXAMPLE 48

Identification of Tissue Types or Cell Species by Means of

Labeled Tissue Specific Antibodies

Identification of specific tissues is accomplished by the visualization of tissue specific antigens by means of
antibody preparations according to Examples 30 and 40 which are conjugated, directly or indirectly to a detectable
marker. Selected labeled antibody species bind to their specific antigen binding partner in tissue sections, cell
suspensions, or in extracts of soluble proteins from a tissue sample to provide a pattern for qualitative or semiqualitative interpretation.

Antisera for these procedures must have a potency exceeding that of the native preparation, and for that

reason, antibodies are concentrated to a mg/ml level by isolation of the gamma globulin fraction, for example, by ionexchange chromatography or by ammonium sulfate fractionation. Also, to provide the most specific antisera, unwanted
antibodies, for example to common proteins, must be removed from the gamma globulin fraction, for example by means
of insoluble immunoabsorbents, before the antibodies are labeled with the marker. Either monoclonal or heterologous
antisera is suitable for either procedure.

A. Immunohistochemical Techniques

Purified, high-titer antibodies, prepared as described above, are conjugated to a detectable marker, as described, for example, by Fudenberg, H., Chap. 26 in: Basic 503 Clinical Immunology, 3rd Ed. Lange, Los Altos, California (1980) or Rose, N. et al., Chap. 12 in: Methods in Immunodiagnosis, 2d Ed. John Wiley 503 Sons, New York (1980).

A fluorescent marker, either fluorescein or rhodamine, is preferred, but antibodies can also be labeled with an enzyme that supports a color producing reaction with a substrate, such as horseradish peroxidase. Markers can be added to tissue-bound antibody in a second step, as described below. Alternatively, the specific antitissue antibodies can be labeled with ferritin or other electron dense particles, and localization of the ferritin coupled antigen-antibody complexes achieved by means of an electron microscope. In yet another approach, the antibodies are radiolabeled, with, for example ¹²⁵I, and detected by overlaying the antibody treated preparation with photographic emulsion.

Preparations to carry out the procedures can comprise monoclonal or polyclonal antibodies to a single protein or peptide identified as specific to a tissue type, for example, brain tissue, or antibody preparations to several antigenically distinct tissue specific antigens can be used in panels, independently or in mixtures, as required.

Tissue sections and cell suspensions are prepared for immunohistochemical examination according to common histological techniques. Multiple cryostat sections (about 4 µm, unfixed) of the unknown tissue and known control, are mounted and each slide covered with different dilutions of the antibody preparation. Sections of known and unknown tissues should also be treated with preparations to provide a positive control, a negative control, for example, pre-immune sera, and a control for non-specific staining, for example, buffer.

Treated sections are incubated in a humid chamber for 30 min at room temperature, rinsed, then washed in buffer for 30-45 min. Excess fluid is blotted away, and the marker developed.

If the tissue specific antibody was not labeled in the first incubation, it can be labeled at this time in a second antibody-antibody reaction, for example, by adding fluorescein- or enzyme-conjugated antibody against the immunoglobulin class of the antiserum-producing species, for example, fluorescein labeled antibody to mouse IgG. Such 25 labeled sera are commercially available.

The antigen found in the tissues by the above procedure can be quantified by measuring the intensity of color or fluorescence on the tissue section, and calibrating that signal using appropriate standards.

B. Identification of Tissue Specific Soluble Proteins

The visualization of tissue specific proteins and identification of unknown tissues from that procedure is

carried out using the labeled antibody reagents and detection strategy as described for immunohistochemistry; however
the sample is prepared according to an electrophoretic technique to distribute the proteins extracted from the tissue in
an orderly array on the basis of molecular weight for detection.

A tissue sample is homogenized using a Virtis apparatus; cell suspensions are disrupted by Dounce homogenization or osmotic lysis, using detergents in either case as required to disrupt cell membranes, as is the practice

in the art. Insoluble cell components such as nuclei, microsomes, and membrane fragments are removed by ultracentrifugation, and the soluble protein-containing fraction concentrated if necessary and reserved for analysis.

A sample of the soluble protein solution is resolved into individual protein species by conventional SDS polyacrylamide electrophoresis as described, for example, by Davis, L. et al., Section 19-2 in: Basic Methods in 5 Molecular Biology (P. Leder, ed), Elsevier, New York (1986), using a range of amounts of polyacrylamide in a set of gels to resolve the entire molecular weight range of proteins to be detected in the sample. A size marker is run in parallel for purposes of estimating molecular weights of the constituent proteins. Sample size for analysis is a convenient volume of from 5 to 55 μ l, and containing from about 1 to 100 μ g protein. An aliquot of each of the resolved proteins is transferred by blotting to a nitrocellulose filter paper, a process that maintains the pattern of resolution. Multiple copies 10 are prepared. The procedure, known as Western Blot Analysis, is well described in Davis, L. et al., (above) Section 19-3. One set of nitrocellulose blots is stained with Coomassie Blue dye to visualize the entire set of proteins for comparison with the antibody bound proteins. The remaining nitrocellulose filters are then incubated with a solution of one or more specific antisera to tissue specific proteins prepared as described in Examples 30 and 40. In this procedure, as in procedure A above, appropriate positive and negative sample and reagent controls are run.

In either procedure A or B, a detectable label can be attached to the primary tissue antigen-primary antibody complex according to various strategies and permutations thereof. In a straightforward approach, the primary specific antibody can be labeled; alternatively, the unlabeled complex can be bound by a labeled secondary anti-lgG antibody. In other approaches, either the primary or secondary antibody is conjugated to a biotin molecule, which can, in a subsequent step, bind an avidin conjugated marker. According to yet another strategy, enzyme labeled or radioactive 20 protein A, which has the property of binding to any IgG, is bound in a final step to either the primary or secondary antibody.

The visualization of tissue specific antigen binding at levels above those seen in control tissues to one or more tissue specific antibodies, prepared from the gene sequences identified from extended cDNA sequences, can identify tissues of unknown origin, for example, forensic samples, or differentiated tumor tissue that has metastasized to foreign 25 bodily sites.

In addition to their applications in forensics and identification, extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to their chromosomal locations. Example 49 below describes radiation hybrid (RH) mapping of human chromosomal regions using extended cDNAs. Example 50 below describes a representative procedure for mapping an extended cDNA (or a genomic DNA obtainable therefrom) to its location on a human chromosome. Example 30 51 below describes mapping of extended cDNAs (or genomic DNAs obtainable therefrom) on metaphase chromosomes by Fluorescence In Situ Hybridization (FISH).

EXAMPLE 49

Radiation hybrid mapping of Extended cDNAs to the human genome

Radiation hybrid (RH) mapping is a somatic cell genetic approach that can be used for high resolution mapping of the human genome. In this approach, cell lines containing one or more human chromosomes are lethally irradiated, breaking each chromosome into fragments whose size depends on the radiation dose. These fragments are rescued by fusion with cultured rodent cells, yielding subclones containing different portions of the human genome. This technique is described by Benham et al. (*Genomics* 4:509-517, 1989) and Cox et al., (*Science* 250:245-250, 1990). The random and independent nature of the subclones permits efficient mapping of any human genome marker. Human DNA isolated from a panel of 80-100 cell lines provides a mapping reagent for ordering extended cDNAs (or genomic DNAs obtainable therefrom). In this approach, the frequency of breakage between markers is used to measure distance, allowing construction of fine resolution maps as has been done using conventional ESTs (Schuler et al., *Science* 274:540-546, 1996).

RH mapping has been used to generate a high-resolution whole genome radiation hybrid map of human chromosome 17q22-q25.3 across the genes for growth hormone (GH) and thyr.idine kinase (TK) (Foster et al., *Genomics* 33:185-192, 1996), the region surrounding the Gorlin syndrome gene (Obermayr et al., *Eur. J. Hum. Genet.* 4:242-245, 1996), 60 loci covering the entire short arm of chromosome 12 (Raeymaekers et al., *Genomics* 29:170-178, 1995), the region of human chromosome 22 containing the neurofibromatosis type 2 locus (Frazer et al., *Genomics* 14:574-584, 1992) and 13 loci on the long arm of chromosome 5 (Warrington et al., *Genomics* 11:701-708, 1991).

EXAMPLE 50

Mapping of Extended cDNAs to Human

Chromosomes using PCR techniques

Extended cDNAs (or genomic DNAs obtainable therefrom) may be assigned to human chromosomes using PCR based methodologies. In such approaches, oligonucleotide primer pairs are designed from the extended cDNA sequence (or the sequence of a genomic DNA obtainable therefrom) to minimize the chance of amplifying through an intron. Preferably, the oligonucleotide primers are 18-23 bp in length and are designed for PCR amplification. The creation of PCR primers from known sequences is well known to those with skill in the art. For a review of PCR technology see Erlich, H.A., PCR Technology; Principles and Applications for DNA Amplification. 1992. W.H. Freeman and Co., New York.

The primers are used in polymerase chain reactions (PCR) to amplify templates from total human genomic DNA. PCR conditions are as follows: 60 ng of genomic DNA is used as a template for PCR with 80 ng of each oligonucleotide primer, 0.6 unit of Taq polymerase, and 1 µCu of a ³²P-labeled deoxycytidine triphosphate. The PCR is performed in a microplate thermocycler (Techne) under the following conditions: 30 cycles of 94°C, 1.4 min; 55°C, 2 min; and 72°C, 2 min; with a final extension at 72°C for 10 min. The amplified products are analyzed on a 6% polyacrylamide sequencing gel and visualized by autoradiography. If the length of the resulting PCR product is identical to the distance between the ends of the primer sequences in the extended cDNA from which the primers are derived, then the PCR reaction is repeated with DNA templates from two panels of human-rodent somatic cell hybrids, BIOS

PCRable DNA (BIOS Corporation) and NIGMS Human-Rodent Somatic Cell Hybrid Mapping Panel Number 1 (NIGMS, Camden, NJ).

PCR is used to screen a series of somatic cell hybrid cell lines containing defined sets of human chromosomes for the presence of a given extended cDNA (or genomic DNA obtainable therefrom). DNA is isolated from the somatic hybrids and used as starting templates for PCR reactions using the primer pairs from the extended cDNAs (or genomic DNAs obtainable therefrom). Only those somatic cell hybrids with chromosomes containing the human gene corresponding to the extended cDNA (or genomic DNA obtainable therefrom) will yield an amplified fragment. The extended cDNAs (or genomic DNAs obtainable therefrom) are assigned to a chromosome by analysis of the segregation pattern of PCR products from the somatic hybrid DNA templates. The single human chromosome present in all cell hybrids that give rise to an amplified fragment is the chromosome containing that extended cDNA (or genomic DNA obtainable therefrom). For a review of techniques and analysis of results from somatic cell gene mapping experiments. (See Ledbetter et al., Genomics 6:475-481 (1990).)

Alternatively, the extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to individual chromosomes using FISH as described in Example 51 below.

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EXAMPLE 51

Mapping of Extended 5' ESTs to Chromosomes

Using Fluorescence in situ Hybridization

Fluorescence in situ hybridization allows the extended cDNA (or genomic DNA obtainable therefrom) to be mapped to a particular location on a given chromosome. The chromosomes to be used for fluorescence in situ hybridization techniques may be obtained from a variety of sources including cell cultures, tissues, or whole blood.

In a preferred embodiment, chromosomal localization of an extended cDNA (or genomic DNA obtainable therefrom) is obtained by FISH as described by Cherif et al. *Vroc. Natl. Acad. Sci. U.S.A.*, 87:6639-6643, 1990).

Metaphase chromosomes are prepared from phytohemagglutinin (PHA)-stimulated blood cell donors. PHA-stimulated lymphocytes from healthy males are cultured for 72 h in RPMI-1640 medium. For synchronization, methotrexate (10 µM) is added for 17 h, followed by addition of 5-bromodeoxyuridine (5-BudR, 0.1 mM) for 6 h. Colcemid (1 µg/ml) is added for the last 15 min before harvesting the cells. Cells are collected, washed in RPMI, incubated with a hypotonic solution of KCI (75 mM) at 37°C for 15 min and fixed in three changes of methanol:acetic acid (3:1). The cell suspension is dropped onto a glass slide and air dried. The extended cDNA (or genomic DNA obtainable therefrom) is labeled with biotin-16 dUTP by nick translation according to the manufacturer's instructions (Bethesda Research

Laboratories, Bethesda, MD), purified using a Sephadex G-50 column (Pharmacia, Upssala, Sweden) and precipitated.

Just prior to hybridization, the DNA pellet is dissolved in hybridization buffer (50% formamide, 2 x SSC, 10% dextran sulfate, 1 mg/ml sonicated salmon sperm DNA, pH 7) and the probe is denatured at 70°C for 5-10 min.

Slides kept at -20°C are treated for 1 h at 37°C with RNase A (100 μ g/ml), rinsed three times in 2 X SSC and dehydrated in an ethanol series. Chromosome preparations are denatured in 70% formamide, 2 X SSC for 2 min at

70°C, then dehydrated at 4°C. The slides are treated with proteinase K (10 μg/100 ml in 20 mM Tris·HCl, 2 mM CaCl₂) at 37°C for 8 min and dehydrated. The hybridization mixture containing the probe is placed on the slide, covered with a coverslip, sealed with rubber cement and incubated overnight in a humid chamber at 37°C. After hybridization and post-hybridization washes, the biotinylated probe is detected by avidin-FITC and amplified with additional layers of biotinylated goat anti-avidin and avidin-FITC. For chromosomal localization, fluorescent R-bands are obtained as previously described (Cherif et al., supra.). The slides are observed under a LEICA fluorescence microscope (DMRXA). Chromosomes are counterstained with propidium iodide and the fluorescent signal of the probe appears as two symmetrical yellow-green spots on both chromatids of the fluorescent R-band chromosome (red). Thus, a particular extended cDNA (or genomic DNA obtainable therefrom) may be localized to a particular cytogenetic R-band on a given
10 chromosome.

Once the extended cDNAs (or genomic DNAs obtainable therefrom) have been assigned to particular chromosomes using the techniques described in Examples 49-51 above, they may be utilized to construct a high resolution map of the chromosomes on which they are located or to identify the chromosomes in a sample.

EXAMPLE 52

15 <u>Use of Extended cDNAs to Construct or Expand Chromosome Maps</u>

Chromosome mapping involves assigning a given unique sequence to a particular chromosome as described above. Once the unique sequence has been mapped to a given chromosome, it is ordered relative to other unique sequences located on the same chromosome. One approach to chromosome mapping utilizes a series of yeast artificial chromosomes (YACs) bearing several thousand long inserts derived from the chromosomes of the organism from which the extended cDNAs (or genomic DNAs obtainable therefrom) are obtained. This approach is described in Ramaiah Nagaraja et al. Genome Research 7:210-222, March 1997. Briefly, in this approach each chromosome is broken into overlapping pieces which are inserted into the YAC vector. The YAC inserts are screened using PCR or other methods to determine whether they include the extended cDNA (or genomic DNA obtainable therefrom) whose position is to be determined. Once an insert has been found which includes the extended cDNA (or genomic DNA obtainable therefrom), the insert can be analyzed by PCR or other methods to determine whether the insert also contains other sequences known to be on the chromosome or in the region from which the extended cDNA (or genomic DNA obtainable therefrom) was derived. This process can be repeated for each insert in the YAC library to determine the location of each of the extended cDNAs (or genomic DNAs obtainable therefrom) relative to one another and to other known chromosomal markers. In this way, a high resolution map of the distribution of numerous unique markers along each of the organisms 30 chromosomes may be obtained.

As described in Example 53 below extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to identify genes associated with a particular phenotype, such as hereditary disease or drug response.

EXAMPLE 53

Identification of genes associated with hereditary diseases or drug response

20.0

19.0

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This example illustrates an approach useful for the association of extended cDNAs (or genomic DNAs obtainable therefrom) with particular phenotypic characteristics. In this example, a particular extended cDNA (or genomic DNA obtainable therefrom) is used as a test probe to associate that extended cDNA (or genomic DNA obtainable therefrom) with a particular phenotypic characteristic.

Extended cDNAs (or genomic DNAs obtainable therefrom) are mapped to a particular location on a human chromosome using techniques such as those described in Examples 49 and 50 or other techniques known in the art. A search of Mendelian Inheritance in Man (V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) reveals the region of the human chromosome which contains the extended cDNA (or genomic DNA obtainable therefrom) to be a very gene rich region containing several known genes and several 10 diseases or phenotypes for which genes have not been identified. The gene corresponding to this extended cDNA (or genomic DNA obtainable therefrom) thus becomes an immediate candidate for each of these genetic diseases.

Cells from patients with these diseases or phenotypes are isolated and expanded in culture. PCR primers from the extended cDNA (or genomic DNA obtainable therefrom) are used to screen genomic DNA, mRNA or cDNA obtained from the patients. Extended cDNAs (or genomic DNAs obtainable therefrom) that are not amplified in the patients can 15 be positively associated with a particular disease by further analysis. Alternatively, the PCR analysis may yield fragments of different lengths when the samples are derived from an individual having the phenotype associated with the disease than when the sample is derived from a healthy individual, indicating that the gene containing the extended cDNA may be responsible for the genetic disease.

VI. Use of Extended cDNAs (or genomic DNAs obtainable therefrom) to Construct Vectors

The present extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to construct secretion vectors capable of directing the secretion of the proteins encoded by genes inserted in the vectors. Such secretion vectors may facilitate the purification or enrichment of the proteins encoded by genes inserted therein by reducing the number of background proteins from which the desired protein must be purified or enriched. Exemplary secretion vectors are described in Example 54 below.

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EXAMPLE 54

Construction of Secretion Vectors

The secretion vectors of the present invention include a promoter capable of directing gene expression in the host cell, tissue, or organism of interest. Such promoters include the Rous Sarcoma Virus promoter, the SV40 promoter, the human cytomegalovirus promoter, and other promoters familiar to those skilled in the art.

A signal sequence from an extended cDNA (or genomic DNA obtainable therefrom), such as one of the signal sequences in SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above, is operably linked to the promoter such that the mRNA transcribed from the promoter will direct the translation of the signal peptide. The host cell, tissue, or organism may be any cell, tissue, or organism which recognizes the signal peptide encoded by the signal sequence in the

extended cDNA (or genomic DNA obtainable therefrom). Suitable hosts include mammalian cells, tissues or organisms, avian cells, tissues, or organisms, insect cells, tissues or organisms, or yeast.

In addition, the secretion vector contains cloning sites for inserting genes encoding the proteins which are to be secreted. The cloning sites facilitate the cloning of the insert gene in frame with the signal sequence such that a fusion 5 protein in which the signal peptide is fused to the protein encoded by the inserted gene is expressed from the mRNA transcribed from the promoter. The signal peptide directs the extracellular secretion of the fusion protein.

The secretion vector may be DNA or RNA and may integrate into the chromosome of the host, be stably maintained as an extrachromosomal replicon in the host, be an artificial chromosome, or be transiently present in the host. Many nucleic acid backbones suitable for use as secretion vectors are known to those skilled in the art, including 10 retroviral vectors, SV40 vectors, Bovine Papilloma Virus vectors, yeast integrating plasmids, yeast episomal plasmids, yeast artificial chromosomes, human artificial chromosomes, P element vectors, baculovirus vectors, or bacterial plasmids capable of being transiently introduced into the host.

The secretion vector may also contain a polyA signal such that the polyA signal is located downstream of the gene inserted into the secretion vector.

After the gene encoding the protein for which secretion is desired is inserted into the secretion vector, the secretion vector is introduced into the host cell, tissue, or organism using calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection, viral particles or as naked DNA. The protein encoded by the inserted gene is then purified or enriched from the supernatant using conventional techniques such as ammonium sulfate precipitation, immunoprecipitation, immunochromatography, size exclusion chromatography, ion exchange 20 chromatography, and hplc. Alternatively, the secreted protein may be in a sufficiently enriched or pure state in the supernatant or growth media of the host to permit it to be used for its intended purpose without further enrichment.

The signal sequences may also be inserted into vectors designed for gene therapy. In such vectors, the signal sequence is operably linked to a promoter such that mRNA transcribed from the promoter encodes the signal peptide. A cloning site is located downstream of the signal sequence such that a gene encoding a protein whose secretion is 25 desired may readily be inserted into the vector and fused to the signal sequence. The vector is introduced into an appropriate host cell. The protein expressed from the promoter is secreted extracellularly, thereby producing a therapeutic effect.

The extended cDNAs or 5' ESTs may also be used to clone sequences located upstream of the extended cDNAs or 5' ESTs which are capable of regulating gene expression, including promoter sequences, enhancer sequences, and 30 other upstream sequences which influence transcription or translation levels. Once identified and cloned, these upstream regulatory sequences may be used in expression vectors designed to direct the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative fashion. Example 55 describes a method for cloning sequences upstream of the extended cDNAs or 5' ESTs.

EXAMPLE 55

Use of Extended cDNAs or 5' ESTs to Clone Upstream

Sequences from Genomic DNA

Sequences derived from extended cDNAs or 5' ESTs may be used to isolate the promoters of the corresponding genes using chromosome walking techniques. In one chromosome walking technique, which utilizes the GenomeWalker™ kit available from Clontech, five complete genomic DNA samples are each digested with a different restriction enzyme which has a 6 base recognition site and leaves a blunt end. Following digestion, oligonucleotide adapters are ligated to each end of the resulting genomic DNA fragments.

For each of the five genomic DNA libraries, a first PCR reaction is performed according to the manufacturer's instructions using an outer adaptor primer provided in the kit and an outer gene specific primer. The gene specific primer 10 should be selected to be specific for the extended cDNA or 5' EST of interest and should have a melting temperature, length, and location in the extended cDNA or 'EST which is consistent with its use in PCR reactions. Each first PCR reaction contains 5ng of genomic DNA, 5 μ l of 10X Tth reaction buffer, 0.2 mM of each dNTP, 0.2 μ M each of outer adaptor primer and outer gene specific primer, 1.1 mM of Mg(OAc)₂, and 1 μ l of the Tth polymerase 50X mix in a total volume of 50 μ l. The reaction cycle for the first PCR reaction is as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 15 72°C (7 cycles) / 2 sec @ 94°C, 3 min @ 67°C (32 cycles) / 5 min @ 67°C.

The product of the first PCR reaction is diluted and used as a template for a second PCR reaction according to the manufacturer's instructions using a pair of nested primers which are located internally on the amplicon resulting from the first PCR reaction. For example, 5 μ l of the reaction product of the first PCR reaction mixture may be diluted 180 times. Reactions are made in a 50 μ l volume having a composition identical to that of the first PCR reaction except 20 the nested primers are used. The first nested primer is specific for the adaptor, and is provided with the GenomeWalker™ kit. The second nested primer is specific for the particular extended cDNA or 5' EST for which the promoter is to be cloned and should have a melting temperature, length, and location in the extended cDNA or 5' EST which is consistent with its use in PCR reactions. The reaction parameters of the second PCR reaction are as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 72°C (6 cycles) / 2 sec @ 94°C, 3 min @ 67°C (25 cycles) / 5 min @ 67°C

The product of the second PCR reaction is purified, cloned, and sequenced using standard techniques. Alternatively, two or more human genomic DNA libraries can be constructed by using two or more restriction enzymes. The digested genomic DNA is cloned into vectors which can be converted into single stranded, circular, or linear DNA. A biotinylated oligonucleotide comprising at least 15 nucleotides from the extended cDNA or 5' EST sequence is hybridized to the single stranded DNA. Hybrids between the biotinylated oligonucleotide and the single stranded DNA containing 30 the extended cDNA or EST sequence are isolated as described in Example 29 above. Thereafter, the single stranded DNA containing the extended cDNA or EST sequence is released from the beads and converted into double stranded DNA using a primer specific for the extended cDNA or 5' EST sequence or a primer corresponding to a sequence included in the cloning vector. The resulting double stranded DNA is transformed into bacteria. DNAs containing the 5' EST or extended cDNA sequences are identified by colony PCR or colony hybridization.

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Once the upstream genomic sequences have been cloned and sequenced as described above, prospective promoters and transcription start sites within the upstream sequences may be identified by comparing the sequences upstream of the extended cDNAs or 5' ESTs with databases containing known transcription start sites, transcription factor binding sites, or promoter sequences.

In addition, promoters in the upstream sequences may be identified using promoter reporter vectors as described in Example 56.

EXAMPLE 56

Identification of Promoters in Cloned Upstream Sequences

The genomic sequences upstream of the extended cDNAs or 5' ESTs are cloned into a suitable promoter 10 reporter vector, such as the pSEAP-Basic, pSEAP-Enhancer, pβgal-Basic, pβgal-Enhancer, or pEGFP-1 Promoter Reporter vectors available from Clontech. Briefly, each of these promoter reporter vectors include multiple cloning sites positioned upstream of a reporter gene encoding a readily assayable protein such as secreted alkaline phosphatase, β galactosidase, or green fluorescent protein. The sequences upstream of the extended cDNAs or 5' ESTs are inserted into the cloning sites upstream of the reporter gene in both orientations and introduced into an appropriate host cell. The 15 level of reporter protein is assayed and compared to the level obtained from a vector which lacks an insert in the cloning site. The presence of an elevated expression level in the vector containing the insert with respect to the control vector indicates the presence of a promoter in the insert. If necessary, the upstream sequences can be cloned into vectors which contain an enhancer for augmenting transcription levels from weak promoter sequences. A significant level of expression above that observed with the vector lacking an insert indicates that a promoter sequence is present in the 20 inserted upstream sequence.

Appropriate host cells for the promoter reporter vectors may be chosen based on the results of the above described determination of expression patterns of the extended cDNAs and ESTs. For example, if the expression pattern analysis indicates that the mRNA corresponding to a particular extended cDNA or 5' EST is expressed in fibroblasts, the promoter reporter vector may be introduced into a human fibroblast cell line.

Promoter sequences within the upstream genomic DNA may be further defined by constructing nested deletions in the upstream DNA using conventional techniques such as Exonuclease III digestion. The resulting deletion fragments can be inserted into the promoter reporter vector to determine whether the deletion has reduced or obliterated promoter activity. In this way, the boundaries of the promoters may be defined. If desired, potential individual regulatory sites within the promoter may be identified using site directed mutagenesis or linker scanning to obliterate 30 potential transcription factor binding sites within the promoter individually or in combination. The effects of these mutations on transcription levels may be determined by inserting the mutations into the cloning sites in the promoter reporter vectors.

EXAMPLE 57

Cloning and Identification of Promoters

Using the method described in Example 55 above with 5' ESTs, sequences upstream of several genes were obtained. Using the primer pairs GGG AAG ATG GAG ATA GTA TTG CCT G (SEQ ID NO:29) and CTG CCA TGT ACA TGA TAG AGA GAT TC (SEQ ID NO:30), the promoter having the internal designation P13H2 (SEQ ID NO:31) was obtained.

5 Using the primer pairs GTA CCA GGGG ACT GTG ACC ATT GC (SEQ ID NO:32) and CTG TGA CCA TTG CTC CCA AGA GAG (SEQ ID NO:33), the promoter having the internal designation P15B4 (SEQ ID NO:34) was obtained.

Using the primer pairs CTG GGA TGG AAG GCA CGG TA (SEQ ID NO:35) and GAG ACC ACA CAG CTA GAC AA (SEQ ID NO:36), the promoter having the internal designation P29B6 (SEQ ID NO:37) was obtained.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags. The upstream sequences were screened for the presence of motifs resembling transcription factor binding sites or known transcription start sites using the computer program MatInspector release 2.0, August 1996.

Figure 9 describes the transcription factor binding sites present in each of these promoters. The columns labeled matrice provides the name of the MatInspector matrix used. The column labeled position provides the 5' postion of the promoter site. Numeration of the sequence starts from the transcription site as determined by matching the genomic sequence with the 5' EST sequence. The column labeled "orientation" indicates the DNA strand on which the site is found, with the + strand being the coding strand as determined by matching the genomic sequence with the sequence of the 5' EST. The column labeled "score" provides the MatInspector score found for this site. The column labeled "length" provides the length of the site in nucleotides. The column labeled "sequence" provides the sequence of the site found.

The promoters and other regulatory sequences located upstream of the extended cDNAs or 5' ESTs may be used to design expression vectors capable of directing the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative manner. A promoter capable of directing the desired spatial, temporal, developmental, and quantitative patterns may be selected using the results of the expression analysis described in Example 26 above. For example, if a promoter which confers a high level of expression in muscle is desired, the promoter sequence upstream of an extended cDNA or 5' EST derived from an mRNA which is expressed at a high level in muscle, as determined by the method of Example 26, may be used in the expression vector.

Preferably, the desired promoter is placed near multiple restriction sites to facilitate the cloning of the desired insert downstream of the promoter, such that the promoter is able to drive expression of the inserted gene. The promoter may be inserted in conventional nucleic acid backbones designed for extrachromosomal replication, integration into the host chromosomes or transient expression. Suitable backbones for the present expression vectors include retroviral backbones, backbones from eukaryotic episomes such as SV40 or Bovine Papilloma Virus, backbones from bacterial episomes, or artificial chromosomes.

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Preferably, the expression vectors also include a polyA signal downstream of the multiple restriction sites for directing the polyadenylation of mRNA transcribed from the gene inserted into the expression vector.

Following the identification of promoter sequences using the procedures of Examples 55-57, proteins which interact with the promoter may be identified as described in Example 58 below.

EXAMPLE 58

Identification of Proteins Which Interact with Promoter Sequences, Upstream Regulatory Sequences, or mRNA

Sequences within the promoter region which are likely to bind transcription factors may be identified by homology to known transcription factor binding sites or through conventional mutagenesis or deletion analyses of reporter plasmids containing the promoter sequence. For example, deletions may be made in a reporter plasmid containing the promoter sequence of interest operably linked to an assayable reporter gene. The reporter plasmids carrying various deletions within the promoter region are transfected into an appropriate host cell and the effects of the deletions on expression levels is assessed. Transcription factor binding sites within the regions in which deletions reduce expression levels may be further localized using site directed mutagenesis, linker scanning analysis, or other techniques familiar to those skilled in the art. Nucleic acids encoding proteins which interact with sequences in the promoter may be identified using one-hybrid systems such as those described in the manual accompanying the Matchmaker One-Hybrid System kit available from Clontech (Catalog No. K1603-1). Briefly, the Matchmaker One-hybrid system is used as follows. The target sequence for which it is desired to identify binding proteins is cloned upstream of a selectable reporter gene and integrated into the yeast genome. Preferably, multiple copies of the target sequences are inserted into the reporter plasmid in tandem.

A library comprised of fusions between cDNAs to be evaluated for the ability to bind to the promoter and the activation domain of a yeast transcription factor, such as GAL4, is transformed into the yeast strain containing the integrated reporter sequence. The yeast are plated on selective media to select cells expressing the selectable marker linked to the promoter sequence. The colonies which grow on the selective media contain genes encoding proteins which bind the target sequence. The inserts in the genes encoding the fusion proteins are further characterized by sequencing. In addition, the inserts may be inserted into expression vectors or in vitro transcription vectors. Binding of the polypeptides encoded by the inserts to the promoter DNA may be confirmed by techniques familiar to those skilled in the art, such as gel shift analysis or DNAse protection analysis.

VII. Use of Extended cDNAs (or Genomic DNAs Obtainable Therefrom) in Gene Therapy

The present invention also comprises the use of extended cDNAs (or genomic DNAs obtainable therefrom) in gene therapy strategies, including antisense and triple helix strategies as described in Examples 57 and 58 below. In antisense approaches, nucleic acid sequences complementary to an mRNA are hybridized to the mRNA intracellularly, thereby blocking the expression of the protein encoded by the mRNA. The antisense sequences may prevent gene expression through a variety of mechanisms. For example, the antisense sequences may inhibit the ability of ribosomes

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to translate the mRNA. Alternatively, the antisense sequences may block transport of the mRNA from the nucleus to the cytoplasm, thereby limiting the amount of mRNA available for translation. Another mechanism through which antisense sequences may inhibit gene expression is by interfering with mRNA splicing. In yet another strategy, the antisense nucleic acid may be incorporated in a ribozyme capable of specifically cleaving the target mRNA.

EXAMPLE 59

Preparation and Use of Antisense Oligonucleotides

The antisense nucleic acid molecules to be used in gene therapy may be either DNA or RNA sequences. They may comprise a sequence complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom).

The antisense nucleic acids should have a length and melting temperature sufficient to permit formation of an intracellular duplex having sufficient stability to inhibit the expression of the mRNA in the duplex. Strategies for designing antisense nucleic acids suitable for use in gene therapy are disclosed in Green et al., Ann. Rev. Biochem. 55:569-597 (1986) and Izant and Weintraub, Cell 36:1007-1015 (1984).

In some strategies, antisense molecules are obtained from a nucleotide sequence encoding a protein by reversing the orientation of the coding region with respect to a promoter so as to transcribe the opposite strand from that which is normally transcribed in the cell. The antisense molecules may be transcribed using in vitro transcription systems such as those which employ T7 or SP6 polymerase to generate the transcript. Another approach involves transcription of the antisense nucleic acids in vivo by operably linking DNA containing the antisense sequence to a promoter in an expression vector.

Alternatively, oligonucleotides which are complementary to the strand normally transcribed in the cell may be synthesized in vitro. Thus, the antisense nucleic acids are complementary to the corresponding mRNA and are capable of hybridizing to the mRNA to create a duplex. In some embodiments, the antisense sequences may contain modified sugar phosphate backbones to increase stability and make them less sensitive to RNase activity. Examples of modifications suitable for use in antisense strategies are described by Rossi et al., Pharmacol. Ther. 50(2):245-254, (1991).

Various types of antisense oligonucleotides complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom) may be used. In one preferred embodiment, stable and semi-stable antisense oligonucleotides described in International Application No. PCT W094/23026 are used. In these molecules, the 3' end or both the 3' and 5' ends are engaged in intramolecular hydrogen bonding between complementary base pairs. These molecules are better able to withstand exonuclease attacks and exhibit increased stability compared to conventional antisense oligonucleotides.

In another preferred embodiment, the antisense oligodeoxynucleotides against herpes simplex virus types 1 and 2 described in International Application No. WO 95/04141.

In yet another preferred embodiment, the covalently cross-linked antisense oligonucleotides described in International Application No. WO 96/31523 are used. These double- or single-stranded oligonucleotides comprise one or

more, respectively, inter- or intra-oligonucleotide covalent cross-linkages, wherein the linkage consists of an amide bond between a primary amine group of one strand and a carboxyl group of the other strand or of the same strand, respectively, the primary amine group being directly substituted in the 2' position of the strand nucleotide monosaccharide ring, and the carboxyl group being carried by an aliphatic spacer group substituted on a nucleotide or nucleotide analog of the other strand or the same strand, respectively.

The antisense oligodeoxynucleotides and oligonucleotides disclosed in International Application No. WO 92/18522 may also be used. These molecules are stable to degradation and contain at least one transcription control recognition sequence which binds to control proteins and are effective as decoys therefor. These molecules may contain "hairpin" structures, "dumbbell" structures, "modified dumbbell" structures, "cross-linked" decoy structures and "loop" structures.

In another preferred embodiment, the cyclic double-stranded oligonucleotides described in European Patent Application No. 0 572 287 A2 are used. These ligated oligonucleotide "dumbbells" contain the binding site for a transcription factor and inhibit expression of the gene under control of the transcription factor by sequestering the factor.

Use of the closed antisense oligonucleotides disclosed in International Application No. WO 92/19732 is also contemplated. Because these molecules have no free ends, they are more resistant to degradation by exonucleases than are conventional oligonucleotides. These oligonucleotides may be multifunctional, interacting with several regions which are not adjacent to the target mRNA.

The appropriate level of antisense nucleic acids required to inhibit gene expression may be determined using in vitro expression analysis. The antisense molecule may be introduced into the cells by diffusion, injection, infection or transfection using procedures known in the art. For example, the antisense nucleic acids can be introduced into the body as a bare or naked oligonucleotide, oligonucleotide encapsulated in lipid, oligonucleotide sequence encapsidated by viral protein, or as an oligonucleotide operably linked to a promoter contained in an expression vector. The expression vector may be any of a variety of expression vectors known in the art, including retroviral or viral vectors, vectors capable of extrachromosomal replication, or integrating vectors. The vectors may be DNA or RNA.

The antisense molecules are introduced onto cell samples at a number of different concentrations preferably between 1x10⁻¹⁰M to 1x10⁻⁴M. Once the minimum concentration that can adequately control gene expression is identified, the optimized dose is translated into a dosage suitable for use in vivo. For example, an inhibiting concentration in culture of 1x10⁻⁷ translates into a dose of approximately 0.6 mg/kg bodyweight. Levels of oligonucleotide approaching 100 mg/kg bodyweight or higher may be possible after testing the toxicity of the oligonucleotide in laboratory animals. It is additionally contemplated that cells from the vertebrate are removed, treated with the antisense oligonucleotide, and reintroduced into the vertebrate.

It is further contemplated that the antisense oligonucleotide sequence is incorporated into a ribozyme sequence to enable the antisense to specifically bind and cleave its target mRNA. For technical applications of ribozyme and antisense oligonucleotides see Rossi et al., *supra*.

In a preferred application of this invention, the polypeptide encoded by the gene is first identified, so that the

effectiveness of antisense inhibition on translation can be monitored using techniques that include but are not limited to
antibody-mediated tests such as RIAs and ELISA, functional assays, or radiolabeling.

The extended cDNAs of the present invention (or genomic DNAs obtainable therefrom) may also be used in gene therapy approaches based on intracellular triple helix formation. Triple helix oligonucleotides are used to inhibit transcription from a genome. They are particularly useful for studying alterations in cell activity as it is associated with a particular gene. The extended cDNAs (or genomic DNAs obtainable therefrom) of the present invention or, more preferably, a portion of those sequences, can be used to inhibit gene expression in individuals having diseases associated with expression of a particular gene. Similarly, a portion of the extended cDNA (or genomic DNA obtainable therefrom) can be used to study the effect of inhibiting transcription of a particular gene within a cell. Traditionally, homopurine sequences were considered the most useful for triple helix strategies. However, homopyrimidine sequences can also inhibit gene expression. Such homopyrimidine oligonucleotides bind to the major groove at homopurine:homopyrimidine sequences. Thus, both types of sequences from the extended cDNA or from the gene corresponding to the extended cDNA are contemplated within the scope of this invention.

EXAMPLE 60

Preparation and use of Triple Helix Probes

The sequences of the extended cDNAs (or genomic DNAs obtainable therefrom) are scanned to identify 10-mer to 20-mer homopyrimidine or homopurine stretches which could be used in triple-helix based strategies for inhibiting gene expression. Following identification of candidate homopyrimidine or homopurine stretches, their efficiency in inhibiting gene expression is assessed by introducing varying amounts of oligonucleotides containing the candidate sequences into tissue culture cells which normally express the target gene. The oligonucleotides may be prepared on an oligonucleotide synthesizer or they may be purchased commercially from a company specializing in custom oligonucleotide synthesis, such as GENSET, Paris, France.

The oligonucleotides may be introduced into the cells using a variety of methods known to those skilled in the art, including but not limited to calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection or native uptake.

Treated cells are monitored for altered cell function or reduced gene expression using techniques such as

Northern blotting, RNase protection assays, or PCR based strategies to monitor the transcription levels of the target
gene in cells which have been treated with the oligonucleotide. The cell functions to be monitored are predicted based
upon the homologies of the target gene corresponding to the extended cDNA from which the oligonucleotide was derived
with known gene sequences that have been associated with a particular function. The cell functions can also be

predicted based on the presence of abnormal physiologies within cells derived from individuals with a particular inherited disease, particularly when the extended cDNA is associated with the disease using techniques described in Example 53.

The oligonucleotides which are effective in inhibiting gene expression in tissue culture cells may then be introduced in vivo using the techniques described above and in Example 59 at a dosage calculated based on the in vitro results, as described in Example 59.

In some embodiments, the natural (beta) anomers of the oligonucleotide units can be replaced with alpha anomers to render the oligonucleotide more resistant to nucleases. Further, an intercalating agent such as ethidium bromide, or the like, can be attached to the 3' end of the alpha oligonucleotide to stabilize the triple helix. For information on the generation of oligonucleotides suitable for triple helix formation see Griffin et al. (Science 245:967-10 971 (1989).

EXAMPLE 61

Use of Extended cDNAs to Express an Encoded Protein in a Host Organism

The extended cDNAs of the present invention may also be used to express an encoded protein in a host organism to produce a beneficial effect. In such procedures, the encoded protein may be transiently expressed in the host organism or stably expressed in the host organism. The encoded protein may have any of the activities described above. The encoded protein may be a protein which the host organism lacks or, alternatively, the encoded protein may augment the existing levels of the protein in the host organism.

A full length extended cDNA encoding the signal peptide and the mature protein, or an extended cDNA encoding only the mature protein is introduced into the host organism. The extended cDNA may be introduced into the host organism using a variety of techniques known to those of skill in the art. For example, the extended cDNA may be injected into the host organism as naked DNA such that the encoded protein is expressed in the host organism, thereby producing a beneficial effect.

Alternatively, the extended cDNA may be cloned into an expression vector downstream of a promoter which is active in the host organism. The expression vector may be any of the expression vectors designed for use in gene therapy, including viral or retroviral vectors.

The expression vector may be directly introduced into the host organism such that the encoded protein is expressed in the host organism to produce a beneficial effect. In another approach, the expression vector may be introduced into cells in vitro. Cells containing the expression vector are thereafter selected and introduced into the host organism, where they express the encoded protein to produce a beneficial effect.

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EXAMPLE 62

Use Of Signal Peptides Encoded By 5' Ests Or Sequences

Obtained Therefrom To Import Proteins Into Cells

The short core hydrophobic region (h) of signal peptides encoded by the 5'ESTS or extended cDNAs derived from the 5'ESTs of the present invention may also be used as a carrier to import a peptide or a protein of interest, so-

called cargo, into tissue culture cells (Lin et al., J. Biol. Chem., 270: 14225-14258 (1995); Du et al., J. Peptide Res., 51: 235-243 (1998); Rojas et al., Nature Biotech., 16: 370-375 (1998)).

When cell permeable peptides of limited size (approximately up to 25 amino acids) are to be translocated across cell membrane, chemical synthesis may be used in order to add the h region to either the C-terminus or the N-terminus to the cargo peptide of interest. Alternatively, when longer peptides or proteins are to be imported into cells, nucleic acids can be genetically engineered, using techniques familiar to those skilled in the art, in order to link the extended cDNA sequence encoding the h region to the 5' or the 3' end of a DNA sequence coding for a cargo polypeptide. Such genetically engineered nucleic acids are then translated either *in vitro* or *in vivo* after transfection into appropriate cells, using conventional techniques to produce the resulting cell permeable polypeptide. Suitable hosts cells are then simply incubated with the cell permeable polypeptide which is then translocated across the membrane.

This method may be applied to study diverse intracellular functions and cellular processes. For instance, it has been used to probe functionally relevant domains of intracellular proteins and to examine protein-protein interactions involved in signal transduction pathways (Lin et al., supra; Lin et al., J. Biol. Chem., 271: 5305-5308 (1996); Rojas et al., J. Biol. Chem., 271: 27456-27461 (1996); Liu et al., Proc. Natl. Acad. Sci. USA, 93: 11819-11824 (1996); Rojas et al., Bioch. Biophys. Res. Commun., 234: 675-680 (1997)).

Such techniques may be used in cellular therapy to import proteins producing therapeutic effects. For instance, cells isolated from a patient may be treated with imported therapeutic proteins and then re-introduced into the host organism.

Alternatively, the h region of signal peptides of the present invention could be used in combination with a nuclear localization signal to deliver nucleic acids into cell nucleus. Such oligonucleotides may be antisense oligonucleotides or oligonucleotides designed to form triple helixes, as described in examples 59 and 60 respectively, in order to inhibit processing and maturation of a target cellular RNA.

EXAMPLE 63

Reassembling & Resequencing of Clones

Full length cDNA clones obtained by the procedure described in Example 27 were double-sequenced. These sequences were assembled and the resulting consensus sequences were then reanalyzed. Open reading frames were reassigned following essentially the same process as the one described in Example 27.

After this reanalysis process a few abnormalities were revealed. The sequences presented in SEQ ID NOs: 47, 73, 79, 89, 91, 96, 126, 128, 134, and 139 are apparently unlikely to be genuine full length cDNAs. These clones are missing a stop codon and are thus more probably 3' truncated cDNA sequences. Similarly, the sequences presented in SEQ ID NOs: 45, 50, 54, 57, 73, 74, 89, 92, 95, 98, 126, 129, 130, 131 and 139 may also not be genuine full length cDNAs based on homology studies with existing protein sequences. Although both of these sequences encode a potential start methionine each could represent a 5' truncated cDNA.

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In addition, SEQ ID NO: 115 was found to be an alternatively spliced transcript and the identities of some of the bases in SEQ ID NO: 131 were corrected.

Finally, after the reassignment of open reading frames for the clones, new open reading frames were chosen in some instances. For example, in the case of SEO ID NOs: 41, 47, 50, 52, 54-56, 58, 59, 61, 74, 75, 79, 84, 89, 91, 92, 96, 98, 103, 105, 106, 126, 129, 131, and 133 the new open reading frames were no longer predicted to contain a signal peptide.

As discussed above, Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-140 and 242-377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of stop codons (listed under the heading Stop Codon Location in Table IV) the locations in SEQ ID NOs: 40-140 and 242-377 of polyA signals (listed under the heading g PolyA Signal Location in Table IV) and the locations of polyA sites (listed under the heading PolyA Site Location in Table IV).

As discussed above, Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 141-241 and 378-513, the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 141-241 and 379-513 in the mature polypeptide created by cleaving the signal peptide from the fall length polypeptide (fourth column). In Table V, and in the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1 and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

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EXAMPLE 64

Functional Analysis of Predicted Protein Sequences

Following double-sequencing, new contigs were assembled for each of the extended cDNAs of the present invention and each was compared to known sequences available at the time of filing. These sequences originate from the following databases: Genbank (release 108 and daily releases up to October, 15, 1998), Genseq (release 32) PIR (release 33) and SwissProt (release 35). The predicted proteins of the present invention matching known proteins were further classified into 3 categories depending on the level of homology.

The first category contains proteins of the present invention exhibiting more than 70% identical amino acid residues on the whole length of the matched protein. They are clearly close homologues which most probably have the same function or a very similar function as the matched protein.

The second category contains proteins of the present invention exhibiting more remote homologies (40 to 70% over the whole protein) indicating that the protein of the present inventionmay have functions similar to those of the homologous protein.

The third category contains proteins exhibiting homology (90 to 100%) to a domain of a known protein indicating that the matched protein and the protein of the invention may share similar features.

It should be noted that the numbering of amino acids in the protein sequences discussed in Figures 10 to 15, and Table VIII, the first methionine encountered is designated as amino acid number 1. In the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1, and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

In addition all of the corrected amino acid sequences (SEQ ED NOs: 141-241 and 378-513) were scanned for the presence of known protein signatures and motifs. This search was performed against the Prosite 15.0 database, using the Proscan software from the GCG package- Functional signatures and their locations are indicated in Table VIII.

15 A) Proteins which are closely related to known proteins

Protein of SEQ ID NO: 217

The protein of SEQ ID NO: 217 encoded by the extended cDNA SEQ ID NO: 116 isolated from lymphocyte shows complete identity to a human protein TFAR19 that may play a role in apoptosis (Genbank accession number AFD14955, SEQ ID NO: 516) as shown by the alignment in figure 10.

Taken together, these data suggest that the protein of SEQ ID NO: 217 may be involved in the control of development and homeostasis. Thus, this protein may be useful in diagnosis and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders, viral infections such as AIDS, neurodegenerative disorders, osteoporosis.

25 Proteins of SEO ID NOs: 174, 175 and 232

The proteins of SEO ID NOs: 174, 175 and 232 encoded by the extended cDNAs SEO ID NOs:. 73, 74 and 131 respectively and isolated from lymphocytes shows complete extensive homologies to a human secreted protein (Genseq accession number W36955, SEO ID NO: 517). As shown by the alignments of figure 11, the amino acid residues are identical to those of the 110 amino acid long matched protein except for positions 51 and 108-110 of the matched protein for the protein of SEO ID NOs: 174, for positions 48, 94 and 108-110 of the matched protein of SEO ID NOs: 175 and for positions 94, and 108-110 of the matched protein for the protein of SEO ID NOs: 232. Proteins of SEO ID NOs: 174 and 232 may represent alternative forms issued from alternative use of polyadenylation signals.

Taken together, these data suggest that the proteins of SEQ ID NOs: 174, 175 and 232 may play a role in cell proliferation and/or differentiation, in immune responses and/or in haematopoeisis. Thus, this protein or part therein,

may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection.

5 Proteins of SEQ ID NO: 231

The protein of SEQ ID NO: 231 encoded by the extended cDNA SEQ ID NO: 130 shows extensive homology with the human E25 protein (Genbank accession number AFO38953, SEQ ID NO: 515). As shown by the alignments in figure 12, the amino acid residues are identical except for position 159 in the 263 amino acid long matched sequence. The matched protein might be involved in the development and differentiation of haematopoietic stem/progenitor cells.

10 In addition, it is the human homologue of a murine protein thought to be involved in chondro-osteogenic differentiation and belonging to a novel multigene family of integral membrane proteins (Deleersnijder et al, J. Biol. Chem., 271: 19475-19482 (1996)).

The protein of invention contains two short segments from positions 1 to 21 and from 100 to 120 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10 : 685-686 (1994)). The first transmembrane domains matches exactly those predicted for the murine E25 protein.

Taken together, these data suggest that the protein of SEQ ID NO: 231 may be involved in cellular proliferation and differentiation. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and embryogenesis disorders.

20 Protein of SEQ ID NO: 196

The protein of SEQ ID NO: 196 encoded by the extended cDNA SEQ ID NO: 95 shows extensive homology with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518) and its murine homologue (Genbank accession number Y11550). As shown by the alignments in figure 13, the amino acid residues are identical except for position 174 in the 399 amino acid long human matched sequence. The matched protein potentially associated to stomatin may act as a G-protein coupled receptor and is likely to be important for the signal transduction in neurons and haematopoietic cells (Mayer et al, Biochem. Biophys. Acta., 1395: 301-308 (1998)).

Taken together, these data suggest that the protein of SEO ID NOs: 196 may be involved in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases cardiovascular disorders, hypertension, renal injury and repair and septic shock.

Protein of SEQ ID NO: 158

The protein of SEQ ID NOs: 158 encoded by the extended cDNA SEQ ID NO: 57 shows homology with the murine subunit 7a of the COP9 complex (Genbank accession number AF071316, SEQ ID NO: 520). As shown by the

alignments in figure 14, the amino acid residues are identical except for positions 90, 172 and 247 in the 275 amino acid long matched sequence. This complex is highly conserved between mammals and higher plants where it has been shown to act as a repressor of photomorphogenesis All the components of the mammalian COP9 complex contain structural features also present in components of the proteasome regulatory complex and the translation initiation complex eIF3 complex, suggesting that the mammalian COP9 complex is an important cellular regulator modulating multiple signaling pathways (Wei et al, Curr. Biol., 8: 919-922 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 158 may be involved in cellular signaling, probably as a subunit of the human COP9 complex. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

Protein of SEQ ID NO: 226

The protein of SEQ ID NO: 226 encoded by the extended cDNA SEQ ID NO: 125 shows homology with the bovine subunit B14.5B of the NADH-ubiquinone oxidureductase complex (Arizmendi *et al., FEBS Lett.*, 313: 80-84 (1992) and Swissprot accession -number Q02827, SEQ ID NO: 514). As shown by the alignments in figure 15, the amino acid residues are identical except for positions 3-4, 6-12, 32-34, 47, 53-55, 67 and 69-74 in the 120 amino acid long matched sequence. This complex is the first of four complexes located in the inner mitochondrial membrane and composing the mitochondrial electron transport chain. Complex I is involved in the dehydrogenation of NADH and the transportation of electrons to coenzyme Q. It is composed of 7 subunits encoded by the mitochondrial genome and 34 subunits encoded by the nuclear genome. It is also thought to play a role in the regulation of apoptosis and necrosis. Mitochondriocytopathies due to complex I deficiency are frequently encountered and affect tissues with a high energy demand such as brain (mental retardation, convulsions, movement disorders), heart (cardiomyopathy, conduction disorders), kidney (Fanconi syndrome), skeletal muscle (exercise intolerance, muscle weakness, hypotonia) and/or eye (opthmaloplegia, ptosis, cataract and retinopathy). For a review on complex I see Smeitink *et al., Hum. Mol. Gent.*, 7: 1573-1579 (1998).

Taken together, these data suggest that the protein of SEQ ID NO: 226 may be part of the mitochondrial energy-generating system, probably as a subunit of the NADH-ubiquinone oxidoreductase complex. Thus, this protein or part therein, may be useful in diagnosing and/or treating several disorders including, but not limited to, brain disorders (mental retardation, convulsions, movement disorders), 'heart disorders (cardiomyopathy, conduction disorders), kidney disorders (Fanconi syndrome), skeletal muscle disorders (exercise intolerance, muscle weakness, hypotonia) and/or eye disorders opthmalmoplegia, ptosis, cataract and retinopathy).

B) Proteins which are remotely related to proteins with known functions

Proteins of SEO ID NOs: 149, 150 and 211

The proteins of SEQ ID NOs: 1.49,150 and 211 encoded by the extended cDNAs SEQ ID NOs: 48, 49 and 110 respectively and found in, skeletal muscle shows homologies with T1/ST2 ligand polypeptide of either human (Genbank accession number U41804 and Genseq accession number W09639) or rodent species (Genbank accession number U41805 and Genseq accession number W09640). These polypeptides are thought to be cytokines that bind to the ST2 receptor, a member of the immunoglobulin family homologous to the interleukin-1 receptor and present on some lymphoma cells. They are predicted to be cell-surface proteins containing a short transmembrane domain. (Gayle et al, J. Biol. Chem., 271: 5784-5789 (1996)). Proteins of SEQ ID NOs: 149, 150 and 211 may represent alternative forms issued from alternative use of polyadenylation signals.

The protein of invention contains two short transmembrane segments from positions 5 to 25 and from 195 to 215 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10:685-686 (1994)). The second transmembrane domain matches exactly those of the matched cell-surface protein.

Taken together, these data suggest that the protein of SEQ ID NOs: 149, 150 and 211 may act as a cytokine, thus may play a role in the regulation of cell growth and differentiation and/or in the regulation of the immune response. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents such as HIV and/or to suppress graft rejection.

Protein of SEQ ID NO: 177

The protein SEQ ID NO: 177 found in testis encoded by the extended cDNA SEQ ID NO: 76 shows homologies to serine protease inhibitor proteins belonging to the pancreatic trypsin inhibitor family (Kunitz) such as the extracellular proteinase inhibitor named chelonianin (Swissprot accession number P00993). The characteristic PROSITE signature of this family is conserved in the protein of the invention (positions 69 to 87) except for a drastic change of the last cysteine residue into an arginine residue.

Taken together, these data suggest that the protein of SEQ ID NO: 177 may be a protease inhibitor, probably
of the Kunitz family. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders
including but not limited to, cancer and neurodegenerative disorders such as Alzheimer's disease.

Protein of SEQ ID NO: 146

The protein SEQ ID NO: 146 encoded by the extended cDNA SEQ ID NO: 45 shows homology to human apolipoprotein L (Genbank accession number AFO19225). The matched protein is a secreted high density lipoprotein associated with apoA-L-containing lipoproteins which play a key role in reverse cholesterol transport.

Taken together, these data suggest that the protein of SEQ ID NO. 146 may play a role in lipid metabolism. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to,

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hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as, coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia.

Protein of SEQ ID NO: 163

The protein SEQ ED NO: 163 encoded by the extended cDNA SEQ ID NO: 62 shows homology to the yeast autophagocytosis protein AUT1 (SwissProt accession number P40344). The matched protein is required for starvation-induced non-specific bulk transport of cytoplasmic proteins to the vacuole.

Taken together, these data suggest that the protein of SEO ID NO: 163 may play a role in protein transport.

Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to,
autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

C) Proteins homologous to a domain of a protein with known function

Protein of SEQ ID NO: 214

The protein of SEQ ID NO: 214 encoded by the extended cDNA SEQ ID NO: 113 and expressed in adult brain shows extensive homology to part of the murine SHYC protein (Genbank accession number AF072697) which is expressed in the developing and embryonic nervous system as well as along the olfactory pathway in adult brains (Köster et al., Neuroscience Letters., 252: 69-71 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 214 may play a role in nervous system development and function. Thus, this protein may be useful in diagnosing and/or treating cancer and/or brain disorders, including neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

Protein of SEQ ID NO: 225

The protein of SEQ ID NO: 225 encoded by the extended cDNA SEQ ID NO: 124 and expressed in adult prostate belong to the phosphatidylethanolainin-binding protein from which it exhibits the characteristic PROSITE signature from positions 90 to 112 (see table VIII). Proteins from this widespread family, from nematodes to fly, yeast, rodent and primate species, bind hydrophobic ligands such as phospholipids and nucleotides. They are mostly expressed in brain and in testis and are thought to play a role in cell growth and/or maturation, in regulation of the sperm maturation, motility and 'in membrane remodeling. They may act either through signal transduction or through oxidoreduction reactions (for a review see Schoentgen and Jollès, FEBS Letters, 369: 22-26 (1995)).

Taken together, these data suggest that the protein of SEQ ID NO: 225 may play a role in cell. Thus, these growth, maturation and in membrane remodeling and/or may be related to male fertility. Thus, this protein may be useful in diagnosing and/or treating cancer, neurodegenerative diseases, and/of, disorders related to male fertility and sterility.

Protein of SEQ ID NO: 153

The protein of SEQ ID NO: 153 encoded by the extended cDNA SEQ ID NO. 52 and expressed in brain exhibits homology to different integral membrane proteins. These membrane proteins include the nematode protein SRE-2 (Swissprot accession number Q09273) that belongs to the multigene SRE family of *C. elegans* receptor-like proteins and a family of tricarboxylate carriers conserved between flies and mammals. One member of this matched family is the rat tricarboxylate carrier (Genbank accession number S70011), an anion transporter localized in the inner membrane of mitochondria and involved in the biosynthesis of fatty acids and cholesterol. The protein of the invention contains a short transmembrane segments from positions 5 to 25 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10:685-686 (1994)).

Taken together, these data suggest that the protein of SEO ID NO: 153 may play a role in signal transduction
and/or in molecule transport. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, immune disorders, cardiovascular disorders, hypertension, renal injury and repair and septic shock

Protein of SEQ ID NO: 213

The protein of SEQ ID NO: 213 encoded by the extended cDNA SEQ ID NO: 112 and expressed in brain exhibits homology with part of the tRNA pseudouridine 55 synthase found in *Escherichia Coli* (Swissprot accession number P09171). This bacterial protein belongs to the NAP57/CBF5/TRUB family of nucleolar proteins found in bacteria, yeasts and mammals involved in rRNA or tRNA biosynthesis, ribosomal subunit assembly and/or centromere/mircotubule binding.

Taken together, these data suggest that the protein of SEQ ID NO: 213 may play a role in rRNA or tRNA biogensis and function. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, hearing loss or disorders linked to chromosomal instability such as dyskeratosis.

Protein of SEQ ED NO: 240

The protein of SEQ ID NO: 240 encoded by the extended cDNA SEQ ID NO: 139 and expressed in brain exhibits homology with a family of eukaryotic cell surface antigens containing 4 transmembrane domains. The PROSITE signature for this family is conserved in the protein of the invention except for a substitution of an alanine residue in place of any of the following hydrophic residues: leucine, valine, isoleucine or methionine (positions 21 to 36).

The protein of the invention contains three short transmembrane segments from positions 6 to 26, 32 to 52

30 and from 56 to 76 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). These transmembrane domains match the last three transmembrane domains of the matched protein family.

Taken together, these data suggest that the protein of SEO ID NO: 240 may play a role in immunological and/or inflammatory responses, probably as a cell surface antigen. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or

inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection.

Protein of SEQ ID NO: 239

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The protein of SEQ ID NO: 239 encoded by the extended cDNA SEQ ID NO: 138 exhibits homology with a conserved region in a family of NA+/H+ exchanger conserved in yeast, nematode and mammals. These cation/proton exchangers are integral membrane proteins with 5 transmembrane segments involved in intracellular pH regulation, maintenance of cell volume, reabsorption of sodium across specialized epithelia, vectorial transport and are also thought to play a role in signal transduction and especially in the induction of cell proliferation and in the induction of apoptosis.

The protein of invention contains four short transmembrane segments from positions 21 to 41, 48 to 68 and from 131 to 151 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). The third and fourth transmembrane domains match the fourth and fifth transmembrane segments of the matched family of proteins.

Taken together, these data suggest that the protein of SEQ ID NO: 239 may play a role in membrane

15 permeability and/or in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair, septic shock as well as disorders of membrane permeability such as diarrhea.

Protein of SEQ ID NO: 200

The protein of SEQ ID NO: 200 encoded by the extended cDNA SEQ ED NO: 99 and expressed in brain exhibits extensive homology to the N-terminus of cell division cycle protein 23 (Genbank accession number AF053977) and also to a lesser extent to its homologue in Saccharomyces cerevisiae. The matched protein is required for chromosome segregation and is part of the anaphae-promoting complex necessary for cell cycle progression to mitosis.

Taken together, these data suggest that the protein of SEQ ID NO: 200 may play a role in cellular mitosis.

25 Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and leukemia.

Protein of SEQ ID NO: 230

The protein of SEQ ID NO: 230 encoded by the extended cDNA SEQ ID NO: 129 exhibits extensive homology to the C-terminus of the eta subunit of T-complex polypeptide 1 conserved from yeasts to mammals, and even complete identity with the last 54 amino acid residues of the human protein (Genbank accession number AF026292). The matched protein is a chaperonin which assists the folding of actins and tubulins in eukaryotic cells upon ATP hydrolysis.

Taken together, these data suggest that the protein of SEO ID NO: 230 may play a role in the folding, transport, assembly and degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several

types of disorders including, but not limited to, cancer, cardiovascular disorders, immune disorders, neurodegenerative disorders, osteoporosis and arthritis.

Protein of SEQ ED NO: 167

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The protein of SEO ID NO: 167 encoded by the extended cDNA SEO ID NO: 66 exhibits homology to a monkey pepsinogen A-4 precursor (Swissprot accession number P27678) and to related members of the aspartyl protease family. The matched protein belongs to a family of widely distributed proteolytic enzymes known to exist in vertebrate, fungi, plants, retroviruses and some plant viruses.

Taken together, these data suggest that the protein of SEO ID NO: 167 may play a role in the degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

Protein of SEQ ID NO: 179

The protein of SEQ ID NO: 179 encoded by the extended cDNA SEQ ID NO: 78 found in testis exhibits

homology to part of mammalian colipase precursors. Colipases are secreted cofactors for pancreatic lipases that allow the lipase to anchor at the water-lipid interface. Colipase plays a crucial role in the intestinal digestion and absorption of dietary fats. The 5 cysteines characteristic for this protein family are conserved in the protein of the invention although the colipase PROSITE signature is not.

Taken together, these data suggest that the protein of SEQ ED NO: 179 may play a role in the lipid metabolism and/or in male fertility. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia, and disorders linked to male fertility.

25 Protein of SEQ ID NO: 227

The protein of SEQ ID NO: 227 encoded by the extended cDNA SEQ ID NO: 126 exhibits extensive homology to the ATP binding region of a whole family of serine/threonine protein kinases belonging to the CDC2/CDC28 subfamily.

The PROSITE signature characteristic for this domain is present in the protein of the invention from positions 10 to 34.

Taken together, these data suggest that the protein of SEQ ED NO: 158 may bind ATP, and even be a protein 30 kinase. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

Although this invention has been described in terms of certain preferred embodiments, other embodiments which will be apparent to those of ordinary skill in the art in view of the disclosure herein are also within the scope of this invention. Accordingly, the scope of the invention is intended to be defined only by reference to the appended claims.

As discussed above, the extended cDNAs of the present invention or portions thereof can be used for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to 10 compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination for expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or 15 potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins or polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit 20 another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing 30 such methods include without limitation "Molecular Cloning; A Laboratory Manual", 2d ed., Cole Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a

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nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

SEQUENCE LISTING FREE TEXT

The following free text appears in the accompanying Sequence Listing:

In vitro transcription product

oligonucleotide

5 promoter

transcription start site

Von Heijne matrix

Score

matinspector prediction

10 name

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TABLE !

	IABLE	
SEQ ID NO. in Present application	Provisional Application Disclosing Sequence	SEQ ID NO. in provisional application
40	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	51
41	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	72
42	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	52
43	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	78
44	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	73
45	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	41
46	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	· · · · · · · · · · · · · · · · · · ·
47	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	67
48	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	82
49	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	80
50	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	81
51		53
52	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	54
53	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	195
54	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	44
55	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	46
56	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	68
	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	48
57	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	55
58	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	49
59	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	50
	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	97
	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	51
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	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	199
	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	53
	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	57
	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	54
	J.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	55
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70 L	J.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	59

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CONT. TABLE I

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71	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	60
72	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	112
73	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	52
74	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	59
75	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	60
76	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	136
77	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	75
78	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	61
79	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	61
80	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	130
81	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	65
82	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	54
83	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	78
84	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	63
85	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	65
86	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	152
87	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	66
88	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	67
89	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	60
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91	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	61
92	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	62
93	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	166
94	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	70
95	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	73
96	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	63
97	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	52
98	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	62
99	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	176
100	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998,	63
101	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	187
102	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	190
103	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	83
104	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	180
105	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	64
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110	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	82
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112	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	43
113	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	46
114	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	47
115	U.S. Provisional Patent Application Serial No. 60/066,677, filed Nov. 13, 1997	53
116	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	58
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133	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	57
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340	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	173
341	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	174
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344	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	177
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363	L.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	196
364	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	197
365	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	1998
366	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	199
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TABLE II: Parameters used for each step of EST analysis

		Search Charac	teristics	Selection Characteristics		
Step	Program	Strand	Parameters	Identity (%))	Length (bp)	
Miscellaneous	Blastn	both	S=61 X-16	90	17	
tRNA	Fasta	both	•	80	60	
rRNA	Blastn	both	S-108	80	40	
mtRNA	Blastn	both	S-108	80	40	
Procaryotic	Blastn	both	S-144	90	40	
Fungal	Blastn	both	S=144	90	40	
Alu	fasta*	both	•	70	40	
L1	Blastn	both	S=72	70	40	
Repeats	Blastn	both	S=72	70	40	
Promoters	Blastn	top	S=54 X=16	90	15⊥	
Vertebrate	fasta*	both	S-108	90	30	
ESTs	Blatsn	both	S=108 X=16	90	30	
Proteins	blastxŋ	top	E-0.001	-		

^{*} use "Quick Fast" Database Scanner

 $^{\,\}boldsymbol{\bot}\,$ alignment further constrained to begin closer than 10bp to EST\5' end

⁵ η using BLOSUM62 substitution matrix

TABLE III: Parameters used for each step of extended cDNA analysis

Search characteristics		Selection characteristics				
Step	Program	Strand	Parameters	Identity (%)	Length (bp)	Comments
miscellaneous •	FASTA	both	-	90	15	
tRNA*	FASTA	both		80	90	
rRNA*	BLASTN	both	S-108	80	40	<u> </u>
mtRNA*	BLASTN	both	S-108	80	40	
Procaryotic*	BLASTN	both	S-144	90	40	
Fungal*	BLASTN	both	S-144	90	40	
Alu*	BLASTN	both	S=72	70	40	max 5 matches, masking
L1'	BLASTN	both	S-72	70	40	max 5 matches, masking
Repeats'	BLASTN	both	S=72	70	40	masking
PolyA	BLAST2N	top	W-6,S-10,E-1000	90	8	in the last 20 nucleotides
Polyadenylati on signal	-	top	AATAAA allowing 1 mismatch			in the 50 nucleotides preceding the 5' end of the polA
Vertebrate*	BLASTN then FASTA	both		90 then 70	30	first BLASTN and then FASTA on matching sequences
ESTs*	BLAST2N	both		90	30	
Geneseq	BLASTN	both	W-8, B-10	90	30	
ORF	BLASTP	top	W-8, B-10			on ORF proteins, max 10 matches
Proteins*	BLASTX	top	E-0.001	70	30	

steps common to EST analysis and using the same algorithms and parameters
 steps also used in EST analysis but with different algorithms and/or parameters

TABLE IV

ld	FCS Location	SigPep Location	Mature Polypeptide Location	Stop Codon Location	PolyA Signal Location	PolyA Site Location
40	7 through 471	7 through 99	100 through 471	472	537 through 542	554 through 568
4.1	168 through 332		168 through 332	333	557 through 562	·
42	51 through 251	51 through 110	111 through 251	252	849 through 854	882 through 895
43	20 through 613	20 through 82	83 through 613	614		
44	12 through 416	12 through 86	87 through 416	417	425 through 430	445 through 458
45	276 through 1040	276 through 485	486 through 1040	1041		2024 through 2036
46	443 through 619	443 through 589	590 through 619	620	1.	1267 through 1276
47	206 through 747		206 through 747	 		
48	36 through 521	36 through 104	105 through 521	522	528 through 533	548 through 561
49	36 through 395	36 through 104	105 through 395	396	599 through 604	619 through 632
50	21 through 41	† 	21 through 41	42	328 through 333	357 through 370
51	35 through 631	35 through 160	161 through 631	632	901 through 906	979 through 994
52	271 through 399		271 through 399	400		979 tillbugh 994
53	103 through 252	103 through 213	214 through 252	253	·	588 through 597
54	2 through 460		2 through 460	461	713 through 718	- <u> </u>
55	31 through 231		31 through 231	232		735 through 748
56	305 through 565		305 through 565	566	769 through 774	690 through 703
57	124 through 873	124 through 378	379 through 873	874	694 through 699	713 through 725
58	135 through 206	. 124 till bogh 370	135 through 206	207	1673 through 1678	1694 through 1705
59	135 through 818		135 through 208		850 through 855	1056 through 1069
60	33 through 290	33 through 92	<u> </u>	819	909 through 914	1071 through 1084
61	485 through 616		93 through 290	291	•	
62			485 through 616	617	•	669 through 682
63	54 through 995	54 through 227	228 through 995	996	1130 through 1135	1181 through 1191
ļ	657 through 923	657 through 896	897 through 923	924	957 through 962	974 through 1008
64	18 through 311	18 through 62	63 through 311	312		•
65	151 through 426	151 through 258	259 through 426	427	505 through 510	527 through 538
66	10 through 1062	10 through 57	58 through 1062	1063	1710 through 1715	1735 through 1747
67	78 through 491	78 through 218	219 through 491	492	1652 through 1657	1673 through 1686
68	69 through 371	69 through 287	288 through 371	372	510 through 515	530 through 542
69	2 through 757	2 through 205	206 through 757	758	•	1160 through 1174
70	2 through 1051	2 through 205	206 through 1051	1052	1,248 through 1253	1272 through 1285
71	2 through 1171	2 through 205	206 through 1171	1172	1368 through 1373	1386 through 1398
72	42 through 611	42 through 287	288 through 611	612	787 through 792	808 through 821
73	62 through 916	62 through 757	758 through 916		•	904 through 916
74	62 through 520	•	62 through 520	521	1124 through 1129	1141 through 1153
75	21 through 167	•	21 through 167	168		
76	22 through 318	22 through 93	94 through 318	319	497 through 502	516 through 526
77	8 through 292	8 through 118	119 through 292	293	317 through 322	339 through 352
78	16 through 378	16 through 84	85 through 378	379	502 through 507	522 through 542

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80	83 through 340	83 through 124	125 through 340	341	573 through 578	607 through 660
81	47 through 541	47 through 220	221 through 541	542		597 through 605
82	46 through 285	46 through 150	151 through 285	286	364 through 369	385 through 396
83	22 through 240	22 through 84	85 through 240	241	397 through 402	421 through 432
84	89 through 382		89 through 382	383	•	408 through 420
85	80 through 415	80 through 142	143 through 415	416	471 through 476	488 through 501
86	152 through 361	152 through 283	284 through 361	362		
87	32 through 307	32 through 70	71 through 307	308	1240 through 1245	1261 through 1272
88	114 through 734	114 through 239	240 through 734	735	768 through 773	793 through 804
89	199 through 802	·	199 through 802	·	780 through 785	791 through 802
90	38 through 1174	38 through 148	149 through 1174	1175	1452 through 1457	1478 through 1490
91	26 through 361		26 through 361	1.	-	350 through 361
92	3 through 131		3 through 131	132	 	591 through 605
93	33 through 185	33 through 80	81 through 185	186	570 through 575	586 through 591
94	184 through 915	184 through 237	238 through 915	916	1119 through 1124	1139 through 1150
95	58 through 1116	58 through 159	160 through 1116	1117	1486 through 1491	1504 through 1513
96	327 through 417		327 through 417	 -	1.	404 through 417
97	63 through 398	63 through 206	207 through 398	399	1.	
98	2 through 163		2 through 163	164	488 through 493	511 through 522
99	13 through 465	13 through 75	76 through 465	466	1.	1.
100	20 through 703	20 through 94	95 through 703	704	1000 through 1005	1023 through 1041
101	103 through 294	103 through 243	244 through 294	295	-	1.
102	81 through 518	81 through 173	174 through 518	519	1.	
103	66 through 326		66 through 326	327	1066 through 1071	1087 through 1098
104	170 through 289	170 through 250	251 through 289	290		
105	36 through 497		36 through 497	498	650 through 655	663 through 685
106	18 through 320		18 through 320	321	539 through 544	542 through 554
107	71 through 1438	71 through 136	137 through 1438	1439	1644 through 1649	1665 through 1678
108	25 through 318	25 through 75	76 through 318	319	452 through 457	482 through 494
109	84 through 332	84 through 170	171 through 332	333		702 through 714
110	32 through 718	32 through 100	101 through 718	719	770 through 775	793 through 805
111	26 through 481	26 through 88	89 through 481	482	755 through 760	775 through 787
112	26 through 562	26 through 187	188 through 562	563	1.	
113	4 through 810	4 through 279	280 through 810	811	858 through 863	881 through 893
114	55 through 459	55 through 120	121 through 459	460	1444 through 1449	1462 through 1475
115	48 through 248	48 through 161	162 through 248	249	283 through 288	308 through 321
116	25 through 399	25 through 186	187 through 399	400		
117	10 through 1137	10 through 72	73 through 1137	1138	1144 through 1149	1162 through 1173
118	72 through 704	72 through 161	162 through 704	705	772 through 777	
119	44 through 505	44 through 223	224 through 505	506		
120	25 through 393	25 through 150	151 through 393	394	734 through 739	757 through 770
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121	58 through 1095	58 through 114	115 through 1095	1096	·	1202 through 1213
122	31 through 660	31 through 90	91 through 660	661	1288 through 1293	1307 through 1318
123	31 through 582	31 through 90	91 through 582	583	816 through 821	840 through 853
124	15 through 695	15 through 80	81 through 695	696	795 through 800	814 through 826
125	74 through 295	74 through 196	197 through 295	296	545 through 550	561 through 571
126	440 through 659	-	440 through 659		601 through 606	
127	38 through 283	38 through 85	86 through 283	284	257 through 262	
128	121 through 477	121 through 288	289 through 477	·		
129	2 through 163	·	2 through 163	164	292 through 297	310 through 323
130	46 through 675	46 through 87	88 through 675	676	1364 through 1369	1383 through 1392
131	62.through 385	·	62 through 385	386	974 through 979	987 through 999
132	422 through 550	422 through 475	476 through 550	551		714 through 725
133	124 through 231	•	124 through 231	232		387 through 400
134	131 through 1053	131 through 169	170 through 1053	-	1019 through 1024	
135	86 through 403	86 through 181	182 through 403	404	1097 through 1102	1117 through 1128
136	37 through 162	37 through 93	94 through 162	163	224 through 229 .	243 through 254
137	31 through 381	31 through 90	91 through 381	382	1.	875 through 886
138	46 through 579	46 through 156	157 through 579	580	•	1.
139	92 through 471	92 through 172	173 through 471	·	454 through 459	458 through 471
140	154 through 675	154 through 498	499 through 675	676	819 through 824	838 through 849
242	18 through 173	18 through 77	78 through 173	174	864 through 869	882 through 893
243	17 through 595	17 through 85	86 through 595	596	820 through 825	840 through 851
244	89 through 334	89 through 130	131 through 334	335	462 through 467	484 through 495
245	21 through 614	21 through 83	84 through 614	615	849 through 854	873 through 884
246	94 through 573	94 through 258	259 through 573	574	862 through 867	886 through 897
247	74 through 397	74 through 127	128 through 397	398	472 through 477	507 through 518
248	51 through 242	51 through 116	117 through 242	243	319 through 324	339 through 350
249	111 through 191	111 through 155	156 through 191	192	965 through 970	986 through 996
250	45 through 602	45 through 107	108 through 602	603	828 through 833	850 through 860
251	24 through 560	24 through 101	102 through 560	561	563 through 568	583 through 593
252	109 through 558	109 through 273	274 through 558	559		1104 through 1114
253	128 through 835	128 through 220	221 through 835	836	1145 through 1150	1170 through 1181
254	59 through 505	59 through 358	359 through 505	506	1042 through 1047	1062 through 1073
255	1 through 207	1 through 147	148 through 207	208	784 through 789	807 through 818
256	12 through 734	12 through 101	102 through 734	735	914 through 919	961 through 971
257	378 through 518	378 through 467	468 through 518	519	607 through 612	628 through 640
258	110 through 304	110 through 193	194 through 304	305	708 through 713	732 through 743
259	201 through 419	201 through 272	273 through 419	420	601 through 606	627 through 637
260	123 through 302	123 through 176	177 through 302	303	1279 through 1284	1301 through 1312
261	98 through 673	98 through 376	377 through 673	674	•	1025 through 1035
262	17 through 463	17 through 232	233 through 463	464	657 through 662	684 through 696
263	263 through 481	263 through 322	323 through 481	482		858 through 868
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264	42 through 299	42 through 101	102 through 299	300		762 through 775
265	198 through 431	198 through 260	261 through 431	432		1064 through 1074
266	279 through 473	279 through 362	363 through 473	474	944 through 949	970 through 981
267	12 through 644	12 through 92	93 through 644	645	1002 through 1007	1020 through 1031
268	91 through 459	91 through 330	331 through 459	460	•	1271 through 1281
269	70 through 327	70 through 147	148 through 327	328	1741 through 1746	1763 through 1774
270	12 through 497	12 through 104	105 through 497	498	935 through 940	955 through 967
271	9D through 383	90 through 200	201 through 383	384	609 through 614	632 through 643
272	332 through 541	332 through 376	377 through 541	542	739 through 744	761 through 773
273	43 through 222	43 through 177	178 through 222	223	530 through 535	555 through 566
274	115 through 231	115 through 180	181 through 231	232	419 through 424	445 through 455
275	232 through 384	232 through 300	301 through 384	385	650 through 655	662 through 673
276	143 through 427	143 through 286	287 through 427	428	606 through 611	628 through 639
277	284 through 463	284 through 379	380 through 463	464	-	762 through 772
278	162 through 671	162 through 398	399 through 671	672	805 through 810	830 through 840
279	63 through 632	63 through 308	309 through 632	633	808 through 813	829 through 840
280	21 through 362	21 through 200	201 through 362	363	821 through 826	838 through 849
281	21 through 503	21 through 344	345 through 503	504	1305 through 1310	1330 through 1341
282	1 through 201	1 through 63	64 through 201	202	637 through 642	660 through 671
283	39 through 1034	39 through 134	135 through 1034	1035	1566 through 1571	1587 through 1597
284	69 through 263	69 through 125	126 through 263	264	1173 through 1178	1196 through 1205
285	115 through 285	115 through 204	205 through 285	286	505 through 510	525 through 536
286	90 through 344	90 through 140	141 through 344	345	500 through 505	515 through 527
287	57 through 311	57 through 107	108 through 311	312	467 through 472	482 through 493
288	96 through 302	96 through 182	183 through 302	303		501 through 514
289	161 through 526	161 through 328	329 through 526	527	•	799 through 811
290	210 through 332	210 through 299	300 through 332	333	594 through 599	613 through 625
291	212 through 361	212 through 319	320 through 361	362	650 through 655	673 through 684
.292	75 through 482	75 through 128	129 through 482	483	595 through 600	618 through 627
293	50 through 631	50 through 244	245 through 631	632	777 through 782	801 through 812
294	154 through 576	154 through 360	361 through 576	577	737 through 742	763 through 775
295	154 through 897	154 through 360	361 through 897	898	1017 through 1022	1044 through 1054
296	146 through 292	146 through 253	254 through 292	293	395 through 400	433 through 444
297	126 through 383	126 through 167	168 through 383 .	384	726 through 731	743 through 754
298	66 through 497	66 through 239	240 through 497	498	594 through 599	618 through 629
299	49 through 411	49 through 96	97 through 411	412	732 through 737	750 through 763
300	49 through 534	49 through 96	97 through 534	535	593 through 598	612 through 623
301	86 through 415	86 through 145	146 through 415	416	540 through 545	560 through 571
302	56 through 268	56 through 100	101 through 268	269	584 through 589	601 through 612
303	32 through 328	32 through 103	104 through 328	329	508 through 513	528 through 539
304	21 through 527	21 through 95	96 through 527	528	921 through 926	953 through 963
305	147 through 647	147 through 374	375 through 647	648		668 through 681

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306 262 through 471 262 through 308 307 through 471 472 663 through 63 307 74 through 1216 74 through 172 173 through 1216 1217 1627 through 308 48 through 164 48 through 89 90 through 164 165 482 through 43 309 185 through 334 185 through 295 296 through 334 335 355 through 31 310 195 through 347 195 through 272 273 through 347 348 1037 through 31 311 90 through 815 90 through 179 180 through 815 816 883 through 81 312 52 through 513 52 through 354 355 through 438 439 682 through 51 313 172 through 438 172 through 354 355 through 438 439 682 through 61 314 148 through 560 148 through 276 277 through 336 367 770 through 77 315 175 through 553 191 through 34 305 through 553 554 766 through 77 316 191 through 560 106 through 216 217 through 560 604 -	1632 1640 through 1652 87 505 through 517 60 392 through 405
308	87 505 through 517 60 392 through 405
309 185 through 334 185 through 295 296 through 334 335 355 through 310 195 through 347 195 through 272 273 through 347 348 1037 through 311 90 through 815 90 through 179 180 through 815 816 883 through 815 312 52 through 513 52 through 231 232 through 513 514 553 through 513 172 through 438 172 through 354 355 through 438 439 682 through 613 148 through 225 226 through 366 367 770 through 773 315 175 through 336 175 through 276 277 through 336 337	60 392 through 405
310	
311 90 through 815 90 through 179 180 through 815 816 883 through 81 312 52 through 513 52 through 231 232 through 513 514 553 through 51 313 172 through 438 172 through 354 355 through 438 439 682 through 61 314 148 through 366 148 through 225 226 through 366 367 770 through 77 315 175 through 336 175 through 276 277 through 336 337 . 316 191 through 553 191 through 304 305 through 553 554 766 through 77 317 106 through 603 106 through 216 217 through 603 604 . 318 47 through 586 47 through 124 125 through 586 587 1583 through 48 319 99 through 371 99 through 290 291 through 371 372 491 through 48 320 44 through 814 44 through 112 113 through 427 428 499 through 56 321 3 through 427 107 through 190 191 through 427 428 <td< td=""><td>1042 1071 through 1082</td></td<>	1042 1071 through 1082
312 52 through 513 52 through 231 232 through 513 514 553 through 61 313 172 through 438 172 through 354 355 through 438 439 682 through 61 314 148 through 366 148 through 225 226 through 366 367 770 through 77 315 175 through 336 175 through 276 277 through 336 337 - 316 191 through 553 191 through 304 305 through 553 554 766 through 77 317 106 through 603 106 through 216 217 through 603 604 - 318 47 through 586 47 through 24 125 through 371 372 491 through 49 319 99 through 371 99 through 290 291 through 371 372 491 through 49 320 44 through 814 44 through 112 113 through 814 815 - 321 3 through 427 107 through 182 183 through 427 428 499 through 50 322 107 through 427 107 through 83 84 through 407 408 1008 through 5	
313 172 through 438 172 through 354 355 through 438 439 682 through 68 314 148 through 366 148 through 225 226 through 366 367 770 through 77 315 175 through 336 175 through 276 277 through 336 337 . 316 191 through 553 191 through 304 305 through 553 554 766 through 77 317 106 through 603 106 through 216 217 through 603 604 . 318 47 through 586 47 through 124 125 through 586 587 1583 through 49 319 99 through 371 99 through 290 291 through 371 372 491 through 49 320 44 through 814 44 through 112 113 through 814 815 . 321 3 through 581 3 through 182 183 through 407 408 1008 through 50 322 107 through 427 107 through 83 84 through 407 408 1008 through 56 323 45 through 332 201 through 251 252 through 332 333 .	88 905 through 916
314 148 through 366 148 through 225 226 through 366 367 770 through 773 315 175 through 336 175 through 276 277 through 336 337 337 336 191 through 553 191 through 304 305 through 553 554 766 through 773 317 106 through 603 106 through 216 217 through 603 604 318 47 through 586 47 through 124 125 through 586 587 1583 through 493 320 44 through 814 44 through 112 113 through 814 815 321 3 through 581 3 through 182 183 through 581 582 322 107 through 427 107 through 190 191 through 427 428 499 through 503 42 through 407 45 through 83 84 through 407 408 1008 through 132 201 through 251 252 through 332 333 325 217 through 543 217 through 255 256 through 543 544 336 through 543 327 29 through 546 18 through 446 18 through 446 447 930 through 83 328 404 through 586 404 through 466 467 through 586 587 1304 through 133 330 59 through 703 59 through 220 221 through 703 704 886 through 89 331 672 through 752 672 through 722 723 through 703 704 886 through 89 331 672 through 752 672 through 722 723 through 311 312 332 through 333 30 through 232 80 through 127 128 through 291 292 367 through 334 91 through 384 196 through 240 241 through 384 385 461 through 466 546 through 590 591 336 54 through 590 54 through 240 241 through 384 385 461 through 466 336 54 through 590 54 through 240 241 through 384 385 461 through 466 336 54 through 590 54 through 240 241 through 384 385 461 through 466 336 54 through 590 54 through 240 241 through 384 385 461 through 466 336 54 through 580 336 54 through 586 336 346 through 345 346 through 846 847 337 337 331 through 346 336 346 through 345 346 through 346 346 through 346 347 347 through 346 346 throug	58 572 through 583
315 175 through 336 175 through 276 277 through 336 337 . 316 191 through 553 191 through 304 305 through 553 554 766 through 77 317 106 through 603 106 through 216 217 through 603 604 . 318 47 through 586 47 through 124 125 through 586 587 1583 through 48 319 99 through 371 99 through 290 291 through 371 372 491 through 49 320 44 through 814 44 through 112 113 through 814 815 . 321 3 through 581 3 through 182 183 through 581 582 . 322 107 through 427 107 through 190 191 through 427 428 499 through 50 323 45 through 407 45 through 83 84 through 407 408 1008 through 56 324 201 through 332 201 through 251 252 through 332 333 . 325 217 through 543 217 through 255 256 through 543 544 . 3	87 685 through 697
316 191 through 553 191 through 304 305 through 553 554 766 through 77 317 106 through 603 106 through 216 217 through 603 604 - 318 47 through 586 47 through 124 125 through 586 587 1583 through 49 319 99 through 371 99 through 290 291 through 371 372 491 through 49 320 44 through 814 44 through 112 113 through 814 815 - 321 3 through 581 3 through 182 183 through 581 582 - 322 107 through 427 107 through 190 191 through 427 428 499 through 50 323 45 through 407 45 through 83 84 through 407 408 1008 through 1 324 201 through 332 201 through 251 252 through 332 333 - 325 217 through 543 217 through 255 256 through 543 544 - 326 18 through 446 18 through 18 119 through 446 447 930 through 89	75 792 through 803
317 106 through 603 106 through 216 217 through 603 604 - 318 47 through 586 47 through 124 125 through 586 587 1583 through 13 319 99 through 371 99 through 290 291 through 371 372 491 through 49 320 44 through 814 44 through 112 113 through 814 815 - 321 3 through 581 3 through 182 183 through 581 582 - 322 107 through 427 107 through 190 191 through 427 428 499 through 50 323 45 through 407 45 through 83 84 through 407 408 1008 through 1 324 201 through 332 201 through 251 252 through 332 333 - 325 217 through 543 217 through 255 256 through 543 544 - 326 18 through 446 18 through 410 141 through 446 447 930 through 89 327 29 through 586 404 through 466 467 through 586 587 1304 through 86	812 through 823
318 47 through 586 47 through 124 125 through 586 587 1583 through 1 319 99 through 371 99 through 290 291 through 371 372 491 through 49 320 44 through 814 44 through 112 113 through 814 815 . 321 3 through 581 3 through 182 183 through 581 582 . 322 107 through 427 107 through 190 191 through 427 428 499 through 50 323 45 through 407 45 through 83 84 through 407 408 1008 through 1 324 201 through 332 201 through 251 252 through 332 333 . 325 217 through 543 217 through 255 256 through 543 544 . 326 18 through 446 18 through 440 141 through 446 447 930 through 89 327 29 through 724 29 through 481 119 through 586 587 1304 through 89 328 404 through 586 404 through 466 467 through 432 433 548 through 89	71 804 through 817
319 99 through 371 99 through 290 291 through 371 372 491 through 49 320 44 through 814 44 through 112 113 through 814 815 . 321 3 through 581 3 through 182 183 through 581 582 . 322 107 through 427 107 through 190 191 through 427 428 499 through 50 323 45 through 407 45 through 83 84 through 407 408 1008 through 1 324 201 through 332 201 through 251 252 through 332 333 . 325 217 through 543 217 through 255 256 through 543 544 . 326 18 through 446 18 through 140 141 through 446 447 930 through 89 327 29 through 586 404 through 466 467 through 586 587 1304 through 18 329 331 through 432 331 through 387 388 through 432 433 548 through 55 330 59 through 703 59 through 220 221 through 703 704 886 through 89 331 672 through 752 672 through 722 723 through 311	1102 through 1112
320 44 through 814 44 through 112 113 through 814 815 . 321 3 through 581 3 through 182 183 through 581 582 . 322 107 through 427 107 through 190 191 through 427 428 499 through 50 323 45 through 407 45 through 83 84 through 407 408 1008 through 1 324 201 through 332 201 through 251 252 through 332 333 . 325 217 through 543 217 through 255 256 through 543 544 . 326 18 through 446 18 through 140 141 through 446 447 930 through 93 327 29 through 724 29 through 118 119 through 724 725 886 through 89 328 404 through 586 404 through 466 467 through 586 587 1304 through 1 329 331 through 432 331 through 387 388 through 432 433 548 through 55 330 59 through 703 59 through 703 704 886 through 89 331 672 through 752 672 through 722 723 through 311 312 332	1588 1614 through 1623
321 3 through 581 3 through 182 183 through 581 582 . 322 107 through 427 107 through 190 191 through 427 428 499 through 50 323 45 through 407 45 through 83 84 through 407 408 1008 through 1 324 201 through 332 201 through 251 252 through 332 333 . 325 217 through 543 217 through 255 256 through 543 544 . 326 18 through 446 18 through 140 141 through 446 447 930 through 93 327 29 through 724 29 through 118 119 through 724 725 886 through 89 328 404 through 586 404 through 466 467 through 586 587 1304 through 1 329 331 through 432 331 through 387 388 through 432 433 548 through 55 330 59 through 703 59 through 703 704 886 through 89 331 672 through 752 672 through 722 723 through 311 312 332 through 33 332 57 through 232 80 through 127 128 through 231 312	96 513 through 524
322 107 through 427 107 through 190 191 through 427 428 499 through 50 323 45 through 407 45 through 83 84 through 407 408 1008 through 1 324 201 through 332 201 through 251 252 through 332 333 - 325 217 through 543 217 through 255 256 through 543 544 - 326 18 through 446 18 through 140 141 through 446 447 930 through 93 327 29 through 724 29 through 118 119 through 724 725 886 through 89 328 404 through 586 404 through 466 467 through 586 587 1304 through 1 329 331 through 432 331 through 387 388 through 432 433 548 through 55 330 59 through 703 59 through 220 221 through 703 704 886 through 89 331 672 through 752 672 through 722 723 through 311 312 332 through 33 332 57 through 311 57 through 128 129 through 232 233 617 through 62 334 91 through 291 91 through 219	978 through 989
323 45 through 407 45 through 83 84 through 407 408 1008 through 1008 through 1008 through 1008 through 1009 through 100	1006 through 1016
324 201 through 332 201 through 251 252 through 332 333 - 325 217 through 543 217 through 255 256 through 543 544 - 326 18 through 446 18 through 140 141 through 446 447 930 through 93 327 29 through 724 29 through 118 119 through 724 725 886 through 89 328 404 through 586 404 through 466 467 through 586 587 1304 through 1 329 331 through 432 331 through 387 388 through 432 433 548 through 55 330 59 through 703 59 through 220 221 through 703 704 886 through 89 331 672 through 752 672 through 722 723 through 752 753 - 332 57 through 311 57 through 128 129 through 311 312 332 through 33 333 80 through 232 80 through 127 128 through 232 233 617 through 62 334 91 through 384 196 through 240 241 through 384 385 461 through	14 516 through 529
325 217 through 543 217 through 255 256 through 543 544 - 326 18 through 446 18 through 140 141 through 446 447 930 through 93 327 29 through 724 29 through 118 119 through 724 725 886 through 89 328 404 through 586 404 through 466 467 through 586 587 1304 through 1 329 331 through 432 331 through 387 388 through 432 433 548 through 55 330 59 through 703 59 through 220 221 through 703 704 886 through 89 331 672 through 752 672 through 722 723 through 752 753 - 332 57 through 311 57 through 128 129 through 311 312 332 through 33 333 80 through 232 80 through 127 128 through 232 233 617 through 62 334 91 through 291 91 through 219 220 through 291 292 367 through 37 335 196 through 384 196 through 240 241 through 384 385	013 1032 through 1042
326 18 through 446 18 through 140 141 through 446 447 930 through 93 327 29 through 724 29 through 118 119 through 724 725 886 through 89 328 404 through 586 404 through 466 467 through 586 587 1304 through 1 329 331 through 432 331 through 387 388 through 432 433 548 through 55 330 59 through 703 59 through 220 221 through 703 704 886 through 89 331 672 through 752 672 through 722 723 through 752 753 - 332 57 through 311 57 through 128 129 through 311 312 332 through 33 333 80 through 232 80 through 127 128 through 232 233 617 through 62 334 91 through 291 91 through 219 220 through 291 292 367 through 37 335 196 through 384 196 through 240 241 through 384 385 461 through 460 336 54 through 590 54 through 227 228 through 590 591	869 through 880
327 29 through 724 29 through 118 119 through 724 725 886 through 89 328 404 through 586 404 through 466 467 through 586 587 1304 through 1. 329 331 through 432 331 through 387 388 through 432 433 548 through 55. 330 59 through 703 59 through 220 221 through 703 704 886 through 89 331 672 through 752 672 through 722 723 through 752 753 - 332 57 through 311 57 through 128 129 through 311 312 332 through 33 333 80 through 232 80 through 127 128 through 232 233 617 through 62 334 91 through 291 91 through 219 220 through 291 292 367 through 37 335 196 through 384 196 through 240 241 through 384 385 461 through 460 336 54 through 590 54 through 227 228 through 590 591 - 337 133 through 846 133 through 345 346 through 846 847 -	1206 through 1217
328 404 through 586 404 through 466 467 through 586 587 1304 through 1 329 331 through 432 331 through 387 388 through 432 433 548 through 55 330 59 through 703 59 through 220 221 through 703 704 886 through 89 331 672 through 752 672 through 722 723 through 752 753 - 332 57 through 311 57 through 128 129 through 311 312 332 through 33 333 80 through 232 80 through 127 128 through 232 233 617 through 62 334 91 through 291 91 through 219 220 through 291 292 367 through 37 335 196 through 384 196 through 240 241 through 384 385 461 through 460 336 54 through 590 54 through 227 228 through 590 591 - 337 133 through 846 133 through 345 346 through 846 847 -	5 948 through 959
329 331 through 432 331 through 387 388 through 432 433 548 through 55 330 59 through 703 59 through 220 221 through 703 704 886 through 89 331 672 through 752 672 through 722 723 through 752 753 - 332 57 through 311 57 through 128 129 through 311 312 332 through 33 333 80 through 232 80 through 127 128 through 232 233 617 through 62 334 91 through 291 91 through 219 220 through 291 292 367 through 37 335 196 through 384 196 through 240 241 through 384 385 461 through 460 336 54 through 590 54 through 227 228 through 590 591 - 337 133 through 846 133 through 345 346 through 846 847 -	1 910 through 920
330 59 through 703 59 through 220 221 through 703 704 886 through 89 331 672 through 752 672 through 722 723 through 752 753 - 332 57 through 311 57 through 128 129 through 311 312 332 through 33 333 80 through 232 80 through 127 128 through 232 233 617 through 62 334 91 through 291 91 through 219 220 through 291 292 367 through 37 335 196 through 384 196 through 240 241 through 384 385 461 through 460 336 54 through 590 54 through 227 228 through 590 591 - 337 133 through 846 133 through 345 346 through 846 847 -	309 1334 through 1344
331 672 through 752 672 through 722 723 through 752 753 - 332 57 through 311 57 through 128 129 through 311 312 332 through 33 333 80 through 232 80 through 127 128 through 232 233 617 through 62 334 91 through 291 91 through 219 220 through 291 292 367 through 37 335 196 through 384 196 through 240 241 through 384 385 461 through 466 336 54 through 590 54 through 227 228 through 590 591 - 337 133 through 846 133 through 345 346 through 846 847 -	3 573 through 585
332 57 through 311 57 through 128 129 through 311 312 332 through 33 333 80 through 232 80 through 127 128 through 232 233 617 through 62 334 91 through 291 91 through 219 220 through 291 292 367 through 37 335 196 through 384 196 through 240 241 through 384 385 461 through 460 336 54 through 590 54 through 227 228 through 590 591 - 337 133 through 846 133 through 345 346 through 846 847 -	1 903 through 914
333 80 through 232 80 through 127 128 through 232 233 617 through 623 334 91 through 291 91 through 219 220 through 291 292 367 through 373 335 196 through 384 196 through 240 241 through 384 385 461 through 466 336 54 through 590 54 through 227 228 through 590 591 - 337 133 through 846 133 through 345 346 through 846 847 -	1150 through 1161
334 91 through 291 91 through 219 220 through 291 292 367 through 373 335 196 through 384 196 through 240 241 through 384 385 461 through 466 336 54 through 590 54 through 227 228 through 590 591 - 337 133 through 846 133 through 345 346 through 846 847 -	7 351 through 363
335 196 through 384 196 through 240 241 through 384 385 461 through 466 336 54 through 590 54 through 227 228 through 590 591 - 337 133 through 846 133 through 345 346 through 846 847 -	2 634 through 645
336 54 through 590 54 through 227 228 through 590 591 - 337 133 through 846 133 through 345 346 through 846 847 -	2 389 through 400
337 133 through 846 133 through 345 346 through 846 847 .	6 485 through 496
	955 through 965
338 138 through 671 139 through 249 240 through 671 672	890 through 901
338 138 through 671 138 through 248 249 through 671 672 1319 through 13	324 1338 through 1347
339 124 through 411 124 through 186 187 through 411 412 948 through 953	3 971 through 983
340 372 through 494 372 through 443 444 through 494 495 708 through 713	3 732 through 745
341 112 through 450 112 through 192 193 through 450 451 1053 through 10	058 1095 through 1106
342 117 through 866 117 through 170 171 through 866 867 1159 through 11	64 1178 through 1190
343 13 through 465 13 through 75 76 through 465 466 1035 through 10	1
344 2 through 718 2 through 76 77 through 718 719 1170 through 11	140 1060 through 1070
345 86 through 709 86 through 361 362 through 709 710 943 through 948	
346 63 through 320 63 through 179 180 through 320 321 771 through 776	75 1203 through 1213
347 299 through 418 299 through 379 380 through 418 419 739 through 744	75 1203 through 1213 963 through 973

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348	186 through 380	186 through 233	234 through 380	381	383 through 388	396 through 409
349	69 through 458	69 through 233	234 through 458	459	564 through 569	602 through 613
350	12 through 638	12 through 263	264 through 638	639	951 through 956	975 through 985
351	282 through 389	282 through 332	333 through 389	390	1413 through 1418	1437 through 1447
352	208 through 339	208 through 294	295 through 339	340		1631 through 1641
353	69 through 557	69 through 224	225 through 557	558	849 through 854	870 through 883
354	134 through 325	134 through 274	275 through 325	326		718 through 729
355	78 through 731	78 through 227	228 through 731	732		1002 through 1013
356	46 through 693	46 through 90	91 through 693	694	937 through 942	962 through 973
357	126 through 527	126 through 182	183 through 527	528	834 through 839	856 through 867
358	66 through 320	66 through 113	114 through 320	321	490 through 495	508 through 519
359	73 through 948	73 through 159	160 through 948	949		1016 through 1028
360	69 through 434	69 through 236	237 through 434	435	419 through 424	441 through 452
361	628 through 804	628 through 711	712 through 804	805		864 through 875
362	70 through 366	70 through 108	109 through 366	367	496 through 501	521 through 531
363	70 through 366	70 through 108	109 through 366	367		1233 through 1244
364	111 through 434	111 through 185	186 through 434	435		618 through 631
365	19 through 567	19 through 63	64 through 567	568	749 through 754	771 through 781
366	19 through 312	19 through 63	64 through 312	313	896 through 901	921 through 931
367	64 through 612	64 through 234	235 through 612	613		839 through 849
368	39 through 458	39 through 80	81 through 458	459	613 through 618	633 through 644
369	9 through 185	9 through 50	51 through 185	186		906 through 918
370	14 through 316	14 through 121	122 through 316	317	442 through 447	458 through 471
371	70 through 1092	70 through 234	235 through 1092	1093	1475 through 1480	1493 through 1504
372	274 through 597	274 through 399	400 through 597	598	731 through 736	754 through 765
373	230 through 469	230 through 307	308 through 469	470	1004 through 1009	1027 through 1040
374	72 through 545	72 through 203	204 through 545	546	·	1151 through 1162
375	36 through 425	36 through 119	120 through 425	426	1215 through 1220	1240 through 1250
376	155 through 751	155 through 340	341 through 751	752	912 through 917	937 through 947
377	46 through 585	46 through 120	121 through 585	586	584 through 589	606 through 619
						oco mougn o 15

TABLE V

		LABLE A	
ld	Full Length Polypeptide Location	Signal Peptide Location	Mature Polypeptide Location
141	-31 through 124	-31 through -1	1 through 124
142	1 through 55	•	1 through 55
143	-20 through 47	-20 through -1	1 through 47
144	-21 through 177	-21 through -1	1 through 177
145	-25 through 110	-25 through -1	1 through 110
146	-70 through 185	-70 through -1	1 through 185
147	-49 through 10	-49 through -1	1 through 10
148	1 through 180		1 through 180
149	-23 through 139	-23 through -1	1 through 139
150	-23 through 97	-23 through -1	1 through 97
151	1 through 7	•	1 through 7
152	-42 through 157	-42 through -1	1 through 157
153	1 through 43		1 through 43
154	-37 through 13	-37 through -1	1 through 13
155	1 through 153	•	1 through 153
156	1 through 67		1 through 67
157	1 through 87	•	1 through 87
158	-85 through 165	-85 through -1	1 through 165
159	1 through 24		1 through 24
160	1 through 228	•	1 through 228
161	-20 through 66	-20 through -1	1 through 66
162	1 through 44		1 through 44
163	-58 through 256	-58 through -1	1 through 256
164	-80 through 9	-80 through -1	1 through 9
165	-15 through 83	-15 through -1	1 through 83
166	-36 through 56	-36 through -1	1 through 56
167	-16 through 335	-16 through -1	1 through 335
168	-47 through 91	-47 through -1	1 through 91
169	-73 through 28	-73 through -1	1 through 28
170	-68 through 184	-68 through -1	1 through 184
171	-68 through 282	-68 through -1	1 through 282
172	-68 through 322	-68 through -1	1 through 322
173	-82 through 108	-82 through -1	1 through 108
174	-232 through 53	-232 through -1	1 through 53
175	1 through 153		1 through 153
176	1 through 49		1 through 49
177	-24 through 75	-24 through -1	1 through 75
178	-37 through 58	-37 through -1	1 through 58
179	-23 through 98	-23 through -1	1 through 98
180	1 through 59		1 through 59
181	-14 through 72	-14 through -1	1 through 72
182	-58 through 107	-58 through -1	1 through 107
183	-35 through 45	-35 through -1	1 through 45
184	-21 through 52	-21 through -1	1 through 52
185	1 through 98		1 through 98
186	-21 through 91	-21 through -1	1 through 91
187	-44 through 26	-44 through -1	1 through 26
188	-13 through 79	-13 through -1	1 through 79
189	-42 through 165	-42 through -1	1 through 165
190	1 through 201		1 through 201

CONT. TABLE V

CUNI. TABL	E V		
191	-37 through 342	-37 through -1	1 through 342
192	1 through 112	·	1 through 112
193	1 through 43		1 through 43
194	-16 through 35	-16 through -1	1 through 35
195	-18 through 226	-18 through -1	1 through 226
196	-34 through 319	-34 through -1	1 through 319
197	1 through 30		1 through 30
198	-48 through 64	-48 through -1	1 through 64
199	1 through 54	•	1 through 54
200	-21 through 130	-21 through -1	1 through 130
201	-25 through 203	-25 through -1	1 through 203
202	-47 through 17	-47 through -1	1 through 17
203	-31 through 115	-31 through -1	1 through 115
204	1 through 87		1 through 87
205	-27 through 13	-27 through -1	1 through 13
206	1 through 154		1 through 154
207	1 through 101		1 through 101
208	-22 through 434	-22 through -1	1 through 434
209	-17 through 81	-17 through -1	1 through 81
210	-29 through 54	-29 through -1	1 through 54
211	-23 through 206	-23 through -1	
212	-21 through 131	-21 through -1	1 through 206
213	-54 through 125	-54 through -1	1 through 131 1 through 125
214	-92 through 177	-92 through -1	
215	-22 through 113	-22 through -1	1 through 177
216	-38 through 29	-38 through -1	1 through 113 1 through 29
217	-54 through 71	-54 through -1	1 through 71
218	-21 through 355	-21 through -1	1 through 355
219	-30 through 181	-30 through -1	1 through 181
220	-60 through 94	-60 through -1	1 through 94
221	-42 through 81	-42 through -1	1 through 81
222	-19 through 327	-19 through -1	1 through 327
223	-20 through 190	-20 through -1	1 through 190
224	-20 through 164	-20 through -1	1 through 164
225	-22 through 205	-22 through -1	1 through 205
226	-41 through 33	-41 through -1	1 through 33
227	1 through 73	·	1 through 73
228	-16 through 66	-16 through -1	1 through 66
229	-56 through 63	-56 through -1	1 through 63
230	1 through 54		1 through 54
231	-14 through 196	-14 through -1	1 through 196
232	1 through 108		1 through 108
233	-18 through 25	-18 through -1	1 through 25
234	1 through 36		1 through 36
235	-13 through 294	-13 through -1	1 through 294
236	-32 through 74	-32 through -1	1 through 74
237	-19 through 23	-19 through -1	1 through 23
238	-20 through 97	-20 through -1	1 through 97
239	-37 through 141	-37 through -1	1 through 141
240	-27 through 99	-27 through -1	1 through 99
241	-115 through 59	-115 through -1	1 through 59
378	-20 through 32	-20 through -1	1 through 32
379	-23 through 170	-23 through -1	1 through 32
380	-14 through 68	-14 through -1	1 through 68
			r through 65

CONT. TABLE V

CONT. TABLE	<u>V</u>		•
381	-21 through 177	-21 through -1	1 through 177
382	-55 through 105	-55 through -1	1 through 105
383	-18 through 90	-18 through -1	1 through 90
384	-22 through 42	-22 through -1	1 through 42
385	-15 through 12	-15 through -1	1 through 12
386	-21 through 165	-21 through -1	1 through 165
387	-26 through 153	-26 through -1	1 through 153
388	-55 through 95	-55 through -1	1 through 95
389	-31 through 205	-31 through -1	1 through 205
390	-100 through 49	-100 through -1	1 through 49
391	-49 through 20	-49 through -1	1 through 20
392	-30 through 211	-30 through -1	1 through 211
393	-30 through 17	-30 through -1	1 through 17
394	-28 through 37	-28 through -1	1 through 37
395	-24 through 49	-24 through -1	1 through 49
396	-18 through 42	-18 through -1	1 through 42
397	-93 through 99	-93 through -1	1 through 99
398	-72 through 77	-72 through -1	
399	-20 through 53	-20 through -1	1 through 77
400	-20 through 66	-20 through -1	1 through 53
401	-20 through 57		1 through 66
402	-21 through 37	21 through -1	1 through 57
403	-27 through 184	-28 through -1	1 through 37
404	-80 through 43	-27 through -1	1 through 184
405	-26 through 60	-80 through -1	1 through 43
406	-28 through 131	-26 through -1	1 through 60
407		-31 through -1	1 through 131
408	-37 through 61 -15 through 55	-37 through -1	1 through 61
409	-45 through 15	-15 through -1	1 through 55
410	-45 through 15	-45 through -1	1 through 15
411		-22 through -1	1 through 17
412	-23 through 28	-23 through -1	1 through 28
413	-48 through 47	-48 through -1	1 through 47
414	-32 through 28 -79 through 91	-32 through -1	1 through 28
415	-82 through 108	•79 through •1	1 through 91
416		-82 through -1	1 through 108
417	-60 through 54	-60 through -1	1 through 54
417	-108 through 53	-108 through -1	1 through 53
419	-21 through 46	-21 through -1	1 through 46
420	-32 through 300	-32 through -1	1 through 300
422	-19 through 46	-19 through -1	1 through 46
	-30 through 27	-30 through -1	1 through 27
423	-17 through 68	·17 through ·1	1 through 68
424	-17 through 68	-17 through -1	1 through 68
425	-29 through 40	-29 through -1	1 through 40
426	-56 through 66	-56 through -1	1 through 66
427	-30 through 11	-30 through -1	1 through 11
428	-36 through 14	-36 through -1	1 through 14
429	-18 through 118	-18 through -1	1 through 118
430	-65 through 129	-65 through -1	1 through 129
431	-69 through 72	-69 through -1	1 through 72
432	-69 through 179	-69 through -1	1 through 179
433	-36 through 13	-36 through -1	1 through 13
434	-14 through 72	-14 through -1	1 through 72
435	-58 through 86	-58 through -1	1 through 86

CONT. TABLE V

CONT. TABLE	V		
436	-16 through 105	-16 through -1	1 through 105
437	-16 through 146	-16 through -1	1 through 146
438	-20 through 90	-20 through -1	1 through 90
439	-15 through 56	-15 through -1	1 through 56
440	-24 through 75	-24 through -1	1 through 75
441	-25 through 144	-25 through -1	1 through 144
442	-76 through 91	-76 through -1	1 through 91
443	-15 through 55	-15 through -1	1 through 55
444	-33 through 348	-33 through -1	1 through 348
445	-14 through 25	-14 through -1	1 through 25
446	-37 through 13	-37 through -1	1 through 13
447	-26 through 25	-26 through -1	1 through 25
448	-30 through 212	-30 through -1	1 through 212
449	-60 through 94	-60 through -1	1 through 94
450	-61 through 28	-61 through -1	1 through 28
451	-26 through 47	-26 through -1	1 through 47
452	-34 through 20	-34 through -1	1 through 20
453	-38 through 83	-38 through -1	1 through 83
454	-37 through 129	-37 through -1	1 through 129
455	-26 through 154	-26 through -1	1 through 154
456	-64 through 27	-64 through -1	1 through 27
457	-23 through 234	-23 through -1	1 through 234
458	-60 through 133	-60 through -1	1 through 133
459	-28 through 79	-28 through -1	1 through 79
460	-13 through 108	-13 through -1	1 through 108
461	-17 through 27	-17 through -1	1 through 27
462	-13 through 96	-13 through -1	1 through 96
463	-41 through 102	-41 through -1	1 through 102
464	-30 through 202	-30 through -1	1 through 202
465	-21 through 40	-21 through -1	1 through 40
466	-19 through 15	·19 through -1	1 through 15
467	-54 through 161	-54 through -1	1 through 161
468	-17 through 10	-17 through -1	1 through 10
469	-24 through 61	-24 through -1	1 through 61
470	-16 through 35	-16 through -1	1 through 35
471	-43 through 24	-43 through -1	1 through 24
472	-15 through 48	-15 through -1	1 through 48
473	-58 through 121	-58 through -1	1 through 121
474	-71 through 167	-71 through -1	1 through 167
475	-37 through 141	-37 through -1	1 through 141
476	-21 through 75	-21 through -1	1 through 75
477	-24 through 17	-24 through -1	1 through 17
478	-27 through 86	-27 through -1	1 through 86
479	-18 through 232	-18 through -1	1 through 232
480	-21 through 130	-21 through -1	1 through 130
481	-25 through 214	-25 through -1	1 through 214
482	-92 through 116	-92 through -1	1 through 116
483	-39 through 47	-39 through -1	1 through 47
484	-27 through 13	-27 through -1	1 through 13
485	-16 through 49	-16 through -1	1 through 49
486	-55 through 75	-55 through -1	1 through 75
487	-84 through 125	-84 through -1	1 through 125
488	-17 through 19	-17 through -1	1 through 19
489	-29 through 15	-29 through -1	. 1 through 15

490	-52 through 111	-52 through -1	1 through 111
491	-47 through 17	-47 through -1	1 through 17
492	-50 through 168	-50 through -1	1 through 168
493	-15 through 201	-15 through -1	1 through 201
494	-19 through 115	-19 through -1	1 through 115
495	-16 through 69	-16 through -1	1 through 69
496	-29 through 263	-29 through -1	1 through 263
497	-56 through 66	-56 through -1	1 through 66
498	-28 through 31	-28 through -1	
499	-13 through 86	-13 through -1	1 through 31
500	-13 through 86	-13 through -1	1 through 86
501	-25 through 83	-25 through -1	1 through 86
502	-15 through 168	-15 through -1	1 through 83
503	-15 through 83	-15 through -1	1 through 168
504	-57 through 126		1 through 83
505	-14 through 126	-57 through -1	1 through 126
506		-14 through -1	1 through 126
	-14 through 45	-14 through -1	1 through 45
507	-36 through 65	-36 through -1	1 through 65
508	-55 through 286	-55 through -1	1 through 286
509	-42 through 66	-42 through -1	1 through 66
510	-26 through 54	-26 through -1	1 through 54
511 ·	-44 through 114	-44 through -1	
512	-28 through 102	-28 through -1	1 through 114
513	-62 through 137	-62 through -1	1 through 102
514	·25 through 155		1 through 137
	20 through 100	-25 through -1	1 through 155

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TABLE VI

ld	Collection refs	Deposit Name
40	ATCC # 98921	SignalTag 121-144
41	ATCC # 98922	
42	ATCC # 98921	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
		SignalTag 121-144
43	ATCC # 98920	SignalTag 67-90
44	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
45	ATCC # 98920	SignalTag 67-90
46	ATCC # 98923	SignalTag 44-66
47	ATCC # 98920	SignalTag 67-90
48	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
49	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
50	ATCC # 98921	SignalTag 121-144
51	ATCC # 98921	SignalTag 121-144
52	ATCC # 98920	SignalTag 67-90
53	ATCC # 98923	SignalTag 44-66
54	ATCC # 98920	SignalTag 67-90
55	ATCC # 98920	SignalTag 67-90
56	ATCC # 98920	SignalTag 67-90
57	ATCC # 98921	SignalTag 121-144
58	ATCC # 98920	SignalTag 67-90
59	ATCC # 98920	SignalTag 67-90
60	ATCC # 98920	SignalTag 67-90
61	ATCC # 98923	SignalTag 44-66
62	ATCC # 98923	SignalTag 44-66
63	ATCC # 98923	SignalTag 44-66
64	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
65	ATCC # 98923	SignalTag 44-66
66	ATCC # 98921	SignalTag 121-144
67	ATCC # 98920	SignalTag 67-90
68	ATCC # 98920	SignalTag 67-90
69	ATCC # 98921	SignalTag 121-144
70	ATCC # 98921	SignalTag 121-144
71	ATCC # 98921	SignalTag 121-144
72	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
73	ATCC # 98923	SignalTag 44-66
	1	orginal ay 44.00

74	ATCC # 98923	SignalTag 44-66
75	ATCC # 98920	SignalTag 67-90
76	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
77	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
78	ATCC # 98921	SignalTag 121-144
79	ATCC # 98923	SignalTag 44-66
80	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
81	ATCC # 98921	SignalTag 121-144
82	ATCC # 98920	SignalTag 67-90
83	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
84	ATCC # 98923	SignalTag 44-66
85	ATCC # 98923	SignalTag 44-66
86	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
87	ATCC # 98923	SignalTag 44-66
88	ATCC # 98923	SignalTag 44-66
89	ATCC # 98923	SignalTag 44-66
90	ATCC # 98923	SignalTag 44-66
91	ATCC # 98923	SignalTag 44-66
92	ATCC # 98920	SignalTag 67-90
93	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
94	ATCC # 98923	SignalTag 44-66
95	ATCC # 98923	SignalTag 44-66
96	ATCC # 98920	SignalTag 67-90
97	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
98	ATCC # 98921	SignalTag 121-144
99	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
100	ATCC # 98921	SignalTag 121-144
101	ATCC # 98920	SignalTag 67-90
102	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
103	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
104	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
105	ATCC # 98921	SignalTag 121-144
106	ATCC # 98920	SignalTag 67-90
107	ATCC # 98920	SignalTag 67-90
108	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
109	ATCC # 98923	SignalTag 44-66
110	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120

,		122
111	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
112	ATCC # 98920	SignalTag 67-90
113	ATCC # 98920	SignalTag 67-90
114	ATCC # 98923	SignalTag 44-66
115	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
116	ATCC # 98920	SignalTag 67-90
117	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
118	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
119	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
120	- ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
121	ATCC # 98923	SignalTag 44-66
122	ATCC # 98920	SignalTag 67-90
123	ATCC # 98920	SignalTag 67-90
124	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
125	ECACC # 98121506	SignalTag 11121998
126	ECACC # 98121506	SignalTag 11121998
127	ECACC # 98121506	SignalTag 11121998
128	ECACC # 98121506	SignalTag 11121998
129	ECACC # 98121506	SignalTag 11121998
130	ECACC # 98121506	SignalTag 11121998
131	ECACC # 98121506	SignalTag 11121998
132	ECACC # 98121506	SignalTag 11121998
133	ECACC # 98121506	SignalTag 11121998
134	ECACC # 98121506	SignalTag 11121998
135	ECACC # 98121506	SignalTag 11121998
136	ECACC # 98121506	SignalTag 11121998
137	ECACC # 98121506	SignalTag 11121998
138	ECACC # 98121506	SignalTag 11121998
139	ECACC # 98121506	SignalTag 11121998
140	ECACC # 98121506	SignalTag 11121998

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TABLE VII

	. 170	LL VII
Internal designation number	SEQ ID NO	Type of sequence
20-5-2-C3-CLO_4	40	DNA
20-8-4-A11-CL2_6	41	DNA
21-1-4-F2-CL11_1	42	DNA
22-11-2-H9-CL1_1	43	DNA
25-7-3-D4-CLO_2	44	DNA
26-27-3-D7-CLO_1	45	DNA
26-35-4-H9-CL1_1	46	DNA
· 26-45-2-C4-CL2_6	47	DNA
27-1-2-B3-CLO_1	48	DNA
27-1-2-B3-CLO_2	49	DNA
27·19·3·G7·CL11_2	50	DNA
33-10-4-E2-CL13_4	51	DNA
33-10-4-H2-CL2_2	52	DNA
33-110-4-A5-CL1_1	53	DNA
33-13-1-C1-CL1_1	54	DNA
33-30-2-A6-CL0_1	55	DNA
33-35-4-F4-CL1_2	56	DNA
33-35-4-G1-CL1_2	57	DNA
33-36-3-E2-CL1_1	58	DNA
33-36-3-E2-CL1_2	59	DNA
33-36-3-F2-CL2_2	60	DNA
33-4-2-G5-CL2_1	61	DNA
33-49-1-H4-CL1_1	62	DNA
33-66-2-B10-CL4_1	63	DNA
33-97-4-G8-CL2_2	64	DNA
33-98-4-C1-CL1_3	-65	DNA
47-14-1-C3-CLO_5	66	DNA
47-15-1-E11-CLO_1	67	DNA
47-15-1-H8-CLO_2	68	DNA
48-1-1-H7-CLO_1	69	DNA
48-1-1-H7-CLO_4	70	DNA
48-1-1-H7-CLO_5	71	DNA
48-3-1-H9-CLO_6	72	DNA
48-54-1-G9-CL2_1	73	DNA

48-54-1-69-CL3_1	74	DNA
48-7-4-H2-CL2_2	75	DNA
51-11-3-D5-CL1_3	76	DNA
51-11-3-G9-CLO_1	77	DNA
51-15-4-A12-CL11_3	78	DNA
51-17-4-A4-CL3_1	79	DNA
51-2-3-F10-CL1_5	80	DNA
51-2-4-F5-CL11_2	81	DNA
51-27-4-F2-CL0_2	82	DNA
51-34-3-F8-CLO_2	83	DNA
57-1-4-E2-CL1_2	84	DNA
57-19-2-G8-CL2_1	85	DNA
57-27-3-G10-CL2_2	86	DNA
58-33-3-B4-CL1_2	87	DNA
58-34-3-C9-CL1_2	88	DNA
58-4-4-G2-CL2_1	89	DNA
58-48-1-G3-CL2_4	90	DNA
58-6-1-H4-CL1_1	91	DNA
60-12-1-E11-CL1_2	92	DNA
65-4-4-H3-CL1_1	93	DNA
74-5-1-E4-CL1_2	94	DNA
76-13-3-A9-CL1_2	95	DNA
76-16-1-D6-CL1_1	96	DNA
76-28-3-A12-CL1_5	97	DNA
76-42-2-F3-CLO_1	98	DNA
77-16-4-G3-CL1_3	99	DNA
77-39-4-H4-CL11_4	100	DNA
78-24-3-H4-CL2_1	101	DNA
78-27-3-D1-CL1_6	102	DNA
78-28-3-D2-CLO_2	103	DNA
78-7-1-G5-CL2_6	104	DNA
84-3-1-G10-CL11_6	105	DNA
58-48-4-E2-CLO_1	106	DNA
23-12-2-G6-CL1_2	107	DNA
25-8-4-B12-CLO_5	108	DNA
26-44-3-C5-CL2_1	109	DNA
27-1-2-B3-CLO_3	110	DNA

		-120-
30-12-3-G5-CLO_1	111	DNA
33-106-2-F10-CL1_3	112	DNA
33-28-4-D1-CLO_1	113	DNA
33-31-3-C8-CL2_1	114	DNA
48-24-1-D2-CL3_2	115	DNA
48-46-4-A11-CL1_4	116	DNA
51-1-4-C1-CLO_2	117	DNA
51-39-3-H2-CL1_2	118	DNA
51-42-3-F9-CL1_1	119	DNA
51-5-3-G2-CLO_4	120	DNA
57-18-4-H5-CL2_1	121	DNA
76-23-3-G8-CL1_1	122	DNA
76-23-3-G8-CL1_3	123	DNA
78-8-3-E6-CLO_1	124	DNA
19-10-1-C2-CL1_3	125	DNA
33-11-1-B11-CL1_2	126	DNA
33-113-2-B8-CL1_2	127	DNA
33-19-1-C11-CL1_1	128	DNA
33-61-2-F6-CLO_2	129	DNA
47-4-4-C6-CL2_2	130	DNA
48-54-1-G9-CL1_1	131	DNA
51-43-3-G3-CL0_1	132	DNA
55-1-3-D11-CL0_1	133	DNA
58-14-2-D3-CL1_2	134	DNA
58-35-2-B6-CL2_3	135	DNA
76-18-1-F6-CL1_1	136	DNA
76-23-3-G8-CL2_2	137	DNA
76-30-3-B7-CL1_1	138	DNA
78-21-3-G7-CL2_1	139	DNA
58-45-4-B11-CL13_2	140	DNA
20-5-2-C3-CL0_4	141	PRT
20-8-4-A11-CL2_6	142	PRT
21-1-4-F2-CL11_1	143	PRT
22-11-2-H9-CL1_1	144	PRT
25-7-3-D4-CLO_2	145	PRT
26-27-3-D7-CLO_1	146	PRT
26-35-4-H9-CL1_1	147	PRT

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26-45-2-C4-CL2_6	148	PRT
27-1-2-B3-CLO_1	149	PRT
27-1-2-B3-CLO_2	150	PRT
27-19-3-G7-CL11_2	151	PRT
33-10-4-E2-CL13_4	152	PRT
33-10-4-H2-CL2_2	153	PRT
33-110-4-A5-CL1_1	154	PRT
33-13-1-C1-CL1_1	155	PRT
33-30-2-A6-CLO_1	156	PRT
33-35-4-F4-CL1_2	157	PRT
33-35-4-G1-CL1_2	158	PRT
33-36-3-E2-CL1_1	159	PRT
33-36-3-E2-CL1_2	160	PRT
33-36-3-F2-CL2_2	161	PRT
33-4-2-G5-CL2_1	162	PRT
33-49-1-H4-CL1_1	163	PRT
33-66-2-B10-CL4_1	164	PRT
33-97-4-G8-CL2_2	165	PRT
33-98-4-C1-CL1_3	166	PRT
47-14-1-C3-CL0_5	167	PRT
47-15-1-E11-CLO_1	168	PRT
47-15-1-H8-CLO_2	169	PRT
48-1-1-H7-CLO_1	170	PRT
48-1-1-H7-CLO_4	171	PRT
48-1-1-H7-CLO_5	172	PRT
48-3-1-H9-CLO_6	173	PRT
48-54-1-G9-CL2_1	174	PRT
48-54-1-G9-CL3_1	175	PRT
48-7-4-H2-CL2_2	176	PRT
51-11-3-D5-CL1_3	177	PRT
51-11-3-G9-CLO_1	178	PRT
51-15-4-A12-CL11_3	179	PRT
51-17-4-A4-CL3_1	180	PRT
51-2-3-F10-CL1_5	181	PRT
51-2-4-F5-CL11_2	182	PRT
51-27-4-F2-CLO_2	183	PRT
51-34-3-F8-CLO_2	184	PRT

57-1-4-E2-CL1_2	185	PRT
57-19-2-G8-CL2_1	186	PRT
57-27-3-G10-CL2_2	187	PRT
58-33-3-B4-CL1_2	188	PRT
58-34-3-C9-CL1_2	189	PRT
58-4-4-G2-CL2_1	190	PRT
58-48-1-G3-CL2_4	191	PRT
58-6-1-H4-CL1_1	192	PRT
60-12-1-E11-CL1_2	193	PRT
< 65-4-4-H3-CL1_1	194	PRT
74-5-1-E4-CL1_2	195	PRT
76-13-3-A9-CL1_2	196	PRT
76-16-1-D6-CL1_1	197	PRT
76-28-3-A12-CL1_5	198	PRT
76-42-2-F3-CL0_1	199	PRT
77-16-4-G3-CL1_3	200	PRT
77-39-4-H4-CL11_4	201	PRT
78-24-3-H4-CL2_1	202	PRT
78-27-3-D1-CL1_6	203	PRT
78-28-3-D2-CLO_2	204	PRT
78-7-1-G5-CL2_6	205	PRT
84-3-1-G10-CL11_6	206	PRT
58-48-4-E2-CLO_1	207	PRT
23-12-2-G6-CL1_2	208	PRT
25-8-4-B12-CL0_5	209	PRT
26-44-3-C5-CL2_1	210	PRT
27-1-2-B3-CL0_3	211	PRT
30-12-3-G5-CLO_1	212	PRT
33-106-2-F10-CL1_3	213	PRT
33-28-4-D1-CLO_1	214	PRT
33-31-3-C8-CL2_1	215	PRT
48-24-1-D2-CL3_2	216	PRT
48-46-4-A11-CL1_4	217	PRT
51-1-4-C1-CL0_2	218	PRT
51-39-3-H2-CL1_2	219	PRT
51-42-3-F9-CL1_1	220	PRT
51-5-3-G2-CLO_4	221	PRT

57-18-4-H5-CL2_1	222	PRT	
76-23-3-G8-CL1_1	223	PRT	
76-23-3-G8-CL1_3	224	PRT	
78-8-3-E6-CLO_1	225	PRT	
19-10-1-C2-CL1_3	226	PRT	
33-11-1-B11-CL1_2	227	PRT	
33-113-2-B8-CL1_2	228	PRT	
33-19-1-C11-CL1_1	229	PRT	
33-61-2-F6-CLO_2	230	PRT	
47-4-4-C6-CL2_2	231	PRT	
48-54-1-G9-CL1_1	232	PRT	
51-43-3-G3-CLO_1	233	PRT	
55-1-3-D11-CLO_1	234	PRT	
58-14-2-D3-CL1_2	235	PRT	
58-35-2-B6-CL2_3	236	PRT	
76-18-1-F6-CL1_1	237	PRT	
76-23-3-68-CL2_2	238	PRT	
76-30-3-B7-CL1_1	239	PRT	
78-21-3-G7-CL2_1	240	PRT	
58-45-4-B11-CL13_2	241	PRT	
20-6-1-D11-FL2	242	DNA	
20-8-4-A11-FL2	243	DNA	
22-6-2-C1-FL2			
22-11-2-H9-FL1			
23-8-3-B1-FL1	246	DNA	
24-3-3-C6-FL1	247	DNA	
24-4-1-H3-FL1	248	DNA	
26-45-2-C4-FL2	249	DNA	
26-48-1-H10-FL1	250	DNA	
26-49-1-A5-FL2	251	DNA	
30-6-4-E3-FL3	252	DNA	
33-6-1-611-FL1	253	DNA	
33-8-1-A3-FL2	254	DNA	
33-11-3-C6-FL1	255	DNA	
33-14-4-E1-FL1	256	DNA	
33-21-2-D5-FL1	257	DNA	
33-26-4-E10-FL1	258	DNA	

33-27-1-E11-FL1	259	DNA	
33-28-4-D1-FL1	260	DNA	
33-28-4-E2-FL2	261	DNA	
33-30-4-C4-FL1	262	DNA	
33-35-4-F4-FL1	263	DNA	
33-36-3-F2-FL2	264	DNA	
33-52-4-F9-FL2	265	DNA	
33-52-4-H3-FL1	266	DNA	
33-59-1-B7-FL1	267	DNA	
33-71-1-A8-FL1	268	DNA	
33-72-2-B2-FL1	269	DNA	
33-105-2-C3-FL1	270	DNA	
33-107-4-C3-FL1	271	DNA	
33-110-2-G4-FL1	272	DNA	
47-7-4-D2-FL2	273	DNA	
47-10-2-G12-FL1	274	DNA	
47-14-3-D8-FL1	275	DNA	
47-18-3-C2-FL1	276	DNA	
47-18-3-G5-FL2	277	DNA	
47-18-4-E3-FL2	278	DNA	
48-3-1-H9-FL3	279	DNA	
48-4-2-H3-FL1	280	DNA	
48-6-1-C9-FL1	281	DNA	
48-7-4-H2-FL2	282	DNA	
48-8-1-D8-FL3	283	DNA	
48-13-3-H8-FL1	284	DNA	
48-19-3-A7-FL1	285	DNA	
48-19-3-G1-FL1	286	DNA	
48-25-4-D8-FL1	287	DNA	
48-21-4-H4-FL1	288	DNA	
48-26-3-B8-FL2	289	DNA	
48-29-1-E2-FL1	290	DNA	
48-31-3-F7-FL1	291	DNA	
48-47-3-A5-FL1	292	DNA	
51-1-1-G12-FL1	293	DNA	
51-1-4-E9-FL3	294	DNA	
51-1-4-E9-FL2	295	DNA	

		. 130-
51-2-1-E10-FL1	296	DNA
51-2-3-F10-FL1	297	DNA
51-2-4-F5-FL1	298	DNA
51-3-3-B10-FL2	299	DNA
51-3-3-B10-FL3	300	DNA
51-7-3-G3-FL1	301	DNA
51-10-3-D11-FL1	302	DNA
51-11-3-D5-FL1	303	DNA
51-13-1-F7-FL3	304	DNA
51-15-4-H10-FL1	305	DNA
51-17-4-A4-FL1	306	DNA
51-18-1-C3-FL1	307	DNA
51-25-3-F3-FL1	308	DNA
51-27-1-E8-FL1	309	DNA
51-28-2-G1-FL2	310	DNA
51-39-3-H2-FL1	311	DNA
51-42-3-F9-FL1	312	DNA
51-44-4-H4-FL1	313	DNA
55-1-3-H10-FL1	314	DNA
55-5-4-A6-FL1	315	DNA
58-26-3-D1-FL1	316	DNA
57-18-1-D5-FL1	317	DNA
57-27-3-A11-FL1	318	DNA
57-27-3-G10-FL2	319	DNA
58-10-3-D12-FL1	320	DNA
58-11-1-G10-FL1	321	DNA
58-11-2-G8-FL2	322	DNA
58-36-3-A9-FL2	323	DNA
58-38-1-A2-FL2	324	DNA
58-38-1-E5-FL1	325	DNA
58-44-2-B3-FL3	326	DNA
58-45-3-H11-FL1	327	DNA
58-53-2-B12-FL2	328	DNA
59-9-4-A10-FL1	329	DNA
60-16-3-A6-FL1	330	DNA
60-17-3-68-FL2	331	DNA
62-5-4-B10-FL1	332	DNA

65-4-4-H3-FL1	333	DNA
74-3-1-B9-FL1	334	DNA
76-4-1-G5-FL1	335	DNA
76-7-3-A12-FL1	336	DNA
76-16-4-C9-FL3	337	DNA
76-30-3-B7-FL1	338	DNA
77-5-1-C2-FL1	339	DNA
77-5-4-E7-FL1	340	DNA
77-11-1-A3-FL1	341	DNA
77-16-3-D7-FL1	342	DNA
77-16-4-G3-FL1	343	DNA
77-25-1-A6-FL1	344	DNA
77-26-2-F2-FL3	345	DNA
78-6-2-E3-FL2	346	DNA
78-7-1-G5-FL2	347	DNA
78-16-2-C2-FL1	348	DNA
78-18-3-B4-FL3	349	DNA
78-20-1-G11-FL1	350	DNA
78-22-3-E10-FL1	351	DNA
78-24-2-B8-FL1	352	DNA
78-24-3-A8-FL1	353	DNA
78-24-3-H4-FL2	354	DNA
78-25-1-F11-FL1	355	DNA
78-26-1-B5-FL1	356	DNA
78-27-3-D1-FL1	357	DNA
78-29-1-B2-FL1	358	DNA
78-29-4-B6-FL1	359	DNA
14-1-3-E6-FL1	360	DNA
30-9-1-G8-FL2	361	DNA
33-10-4-H2-FL2	362	DNA
33-10-4-H2-FL1	363	DNA
74-10-3-C9-FL2	364	DNA
33-97-4-G8-FL3	365	DNA
33-97-4-G8-FL2	366	DNA
33-104-4-H4-FL1	367	DNA
47-2-3-B3-FL1	368	DNA
47-37-4-G11-FL1	369	DNA

57-25-1-F10-FL2	370	DNA
58-19-3-D3-FL1	371	DNA
58-34-3-C9-FL2	372	DNA
58-48-4-E2-FL2	373	DNA
76-21-1-C4-FL1	374	DNA
78-26-2-H7-FL1	375	DNA
77-20-2-E11-FL1	376	DNA
47-1-3-F7-FL2	377	DNA
20-6-1-D11-FL2	378	PRT
20-8-4-A11-FL2	379	PRT
22-6-2-C1-FL2	380	PRT
22-11-2-H9-FL1	381	PRT
23-8-3-B1-FL1	382	PRT
24-3-3-C6-FL1	383	PRT
24-4-1-H3-FL1	384	PRT
26-45-2-C4-FL2	385	PRT
26-48-1-H10-FL1	386	PRT
26-49-1-A5-FL2	387	PRT
30-6-4-E3-FL3	388	PRT
33-6-1-G11-FL1	389	PRT
33-8-1-A3-FL2	390	PRT
33-11-3-C6-FL1	391	PRT
33-14-4-E1-FL1	392	PRT
33-21-2-D5-FL1	393	PRT
33-26-4-E10-FL1	394	PRT
33-27-1-E11-FL1	395	PRT
33-28-4-D1-FL1	396	PRT
33-28-4-E2-FL2	397	PRT
33-30-4-C4-FL1	398	PRT
33-35-4-F4-FL1	399	PRT
33-36-3-F2-FL2	400	PRT
33-52-4-F9-FL2	401.	PRT
33-52-4-H3-FL1	402	PRT
33-59-1-B7-FL1	403	PRT
33-71-1-A8-FL1	404	PRT
33-72-2-B2-FL1	405	PRT
33-105-2-C3-FL1	406	PRT

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33-107-4-C3-FL1	407	PRT	
33-110-2-G4-FL1	408	PRT	
47-7-4-D2-FL2	409	PRT	
47-10-2-G12-FL1	410	PRT	
47-14-3-D8-FL1	411	PRT	
47-18-3-C2-FL1	412	PRT	
47-18-3-G5-FL2	413	PRT	
47-18-4-E3-FL2	414	PRT	
48-3-1-H9-FL3	415	PRT	
48-4-2-H3-FL1	416	PRT	
48-6-1-C9-FL1	417	PRT	
48-7-4-H2-FL2	418	PRT	
48-8-1-D8-FL3	419	PRT	
48-13-3-H8-FL1	420	PRT	
48-19-3-A7-FL1	421	PRT	
48-19-3-G1-FL1	422	PRT	
48-25-4-D8-FL1	423	PRT	
48-21-4-H4-FL1	424	PRT	
48-26-3-B8-FL2	425	PRT	
48-29-1-E2-FL1	426	PRT	
48-31-3-F7-FL1	427	PRT	
48-47-3-A5-FL1	428	PRT	
51-1-1-G12-FL1	429	PRT	
51-1-4-E9-FL3	430	PRT	
51-1-4-E9-FL2	431	PRT	
51-2-1-E10-FL1	432	PRT	
51-2-3-F10-FL1	433	PRT	
51-2-4-F5-FL1	434	PRT	
51-3-3-B10-FL2	435	PRT	
51-3-3-B10-FL3	436	PRT	
51-7-3-63-FL1	437	PRT	
51-10-3-D11-FL1	438	PRT	
51-11-3-D5-FL1	439	PRT	
51-13-1-F7-FL3	440	PRT	
51-15-4-H10-FL1	441	PRT	
51-17-4-A4-FL1	442	PRT	
51-18-1-C3-FL1	443		

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51-25-3-F3-FL1	444	PRT
51-27-1-E8-FL1	445	PRT
51-28-2-G1-FL2	446	PRT
51-39-3-H2-FL1	447	PRT
51-42-3-F9-FL1	448	PRT
51-44-4-H4-FL1	449	PRT
55-1-3-H10-FL1	450	PRT
55-5-4-A6-FL1	451	PRT
58-26-3-D1-FL1	452	PRT
57-18-1-D5-FL1	453	PRT
57-27-3-A11-FL1	454	PRT
57-27-3-G10-FL2	455	PRT
58-10-3-D12-FL1	456	PRT
58-11-1-G10-FL1	457	PRT
58-11-2-G8-FL2	458	PRT
58-36-3-A9-FL2	459	PRT
58-38-1-A2-FL2	460	PRT
58-38-1-E5-FL1	461	PRT
58-44-2-B3-FL3	462	PRT
58-45-3-H11-FL1	463	PRT
58-53-2-B12-FL2	464	PRT
59-9-4-A10-FL1	465	PRT
60-16-3-A6-FL1	466	PRT
60-17-3-G8-FL2	467	PRT
62-5-4-B10-FL1	468	PRT
65-4-4-H3-FL1	469	PRT
74-3-1-B9-FL1	470	PRT
76-4-1-G5-FL1	471	PRT
76-7-3-A12-FL1	472	PRT
76-16-4-C9-FL3	473	PRT
76-30-3-B7-FL1	474	PRT
77-5-1-C2-FL1	475	PRT
77-5-4-E7-FL1	476	PRT
77-11-1-A3-FL1	477	PRT
77-16-3-D7-FL1	478	PRT
77-16-4-G3-FL1	479	PRT
77-25-1-A6-FL1	480	PRT

77-26-2-F2-FL3	481	PRT
78-6-2-E3-FL2	482	PRT
78-7-1-G5-FL2	483	PRT
78-16-2-C2-FL1	484	PRT
78-18-3-B4-FL3	485	PRT
78-20-1-G11-FL1	486	PRT
78-22-3-E10-FL1	487	PRT
78-24-2-B8-FL1	488	PRT
78-24-3-A8-FL1	489	PRT
78-24-3-H4-FL2	490	PRT
78-25-1-F11-FL1	491	PRT
78-26-1-B5-FL1	492	PRT
78-27-3-D1-FL1	493	PRT
78-29-1-B2-FL1	494	PRT
78-29-4-B6-FL1	495	PRT
14-1-3-E6-FL1	496	PRT
30-9-1-G8-FL2	497	PRT
33-10-4-H2-FL2	498	PRT
33-10-4-H2-FL1	499	PRT
74-10-3-C9-FL2	500	PRT
33-97-4-G8-FL3	501	PRT
33-97-4-G8-FL2	502	PRT
33-104-4-H4-FL1	503	PRT
47-2-3-B3-FL1	504	PRT
47-37-4-G11-FL1	505	PRT
57-25-1-F10-FL2	506	PRT
58-19-3-D3-FL1	507	PRT
58-34-3-C9-FL2	508	PRT
58-48-4-E2-FL2	509	PRT
76-21-1-C4-FL1	510	PRT
78-26-2-H7-FL1	511	PRT
77-20-2-E11-FL1	512	PRT
47-1-3-F7-FL2	513	PRT

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TABLE VIII

ID	Locations	PROSITE Signature Name
195	110-121	Aldehyde dehydrogenases csyteine active site
221	28-37	ATP synthase alpha and beta subunits signature
223	171-181	Regulator of chromosome condensation (RCC1) signature 2
225	90-112	Phosphatidylethanolamine-binding protein family signature
226	10-34	Protein kinases ATP-binding region signature

ad tengang di papahan ang kanang di panggalang di manggalang til manggalang

WHAT IS CLAIMED IS:

- A purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto.
- 2. A purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of 5 SEO ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto.
 - 3. A purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID NOs: 40, 42-44, 46, 48, 49, 51, 53, 60, 62-72, 76-78, 80-83, 85-88, 90, 93, 94, 97, 99-102, 104, 107-125, 127, 132, 135-138, 140 and 242-377 wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein.
- 4. A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-44, 46, 48,
 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.
- A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40, 42-46, 48,
 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140
 and 242-377 which encode the signal peptide.
 - 6. A purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 141-241 and 378-513.
- A purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEO ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-20
 189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
 - 8. A purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEO ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
 - A purified or isolated protein comprising the sequence of one of SEQ ID NOs: 141-241 and 378-513.
- 25 10. A purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513.
 - 11. An isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
- An isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
 - 13. A method of making a protein comprising one of the sequences of SEQ ID ND: 141-241 and 378-513, comprising the steps of:

cDNA.

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obtaining a cDNA comprising one of the sequences of sequence of SEO ID NO: 40-140 and 242-377; inserting said cDNA in an expression vector such that said cDNA is operably linked to a promoter; and introducing said expression vector into a host cell whereby said host cell produces the protein encoded by said

- The method of Claim 13, further comprising the step of isolating said protein.
 - 15. A protein obtainable by the method of Claim 14.
 - 16. A host cell containing a recombinant nucleic acid of Claim 1.
- 17. A purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 141-241 and 378-513.
- 10 18. In an array of polynucleotides of at least 15 nucleotides in length, the improvement comprising inclusion in said array of at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides.
- A purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent
 conditions to the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-140 and 242-377.
 - 20. A purified or isolated antibody capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NOs: 141-241 and 378-513.

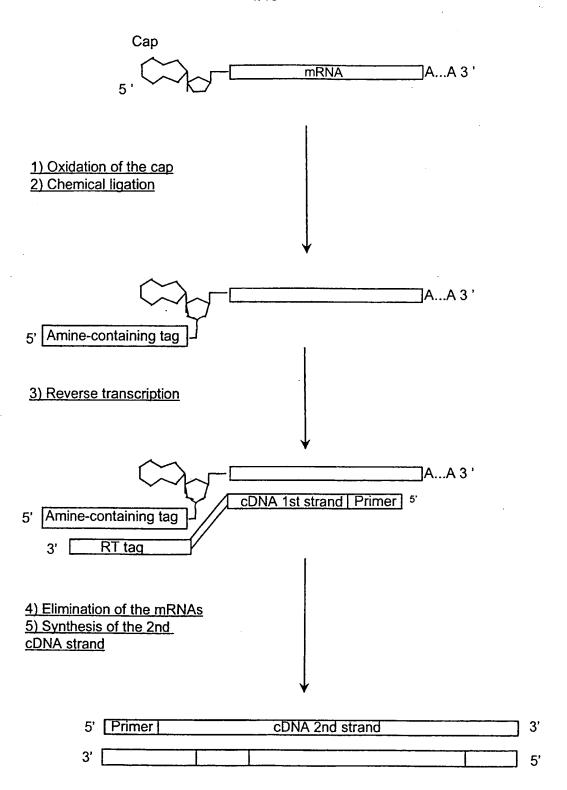
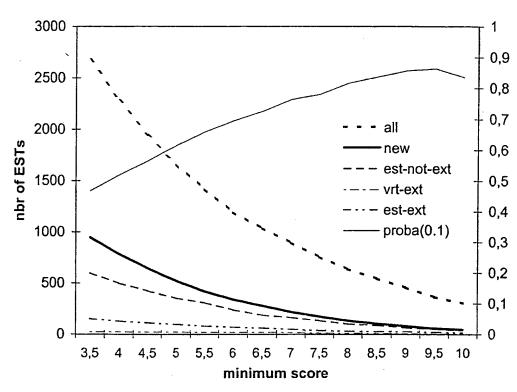


Figure 1

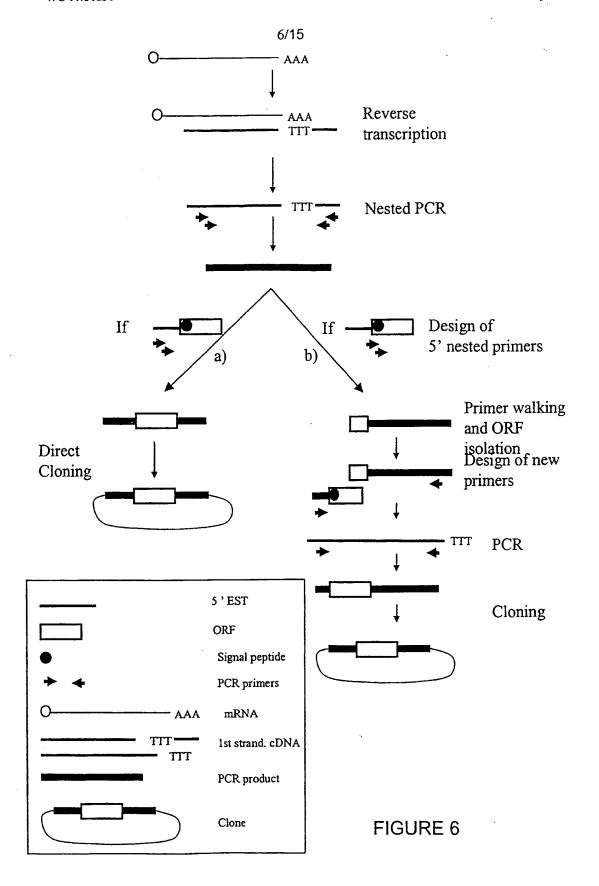
Minimum signal peptide score	false positive rate	false negative rate	proba(0.1)	proba(0.2)
3,5	0,121	0,036	0,467	0,664
4	0,096	0,06	0,519	0,708
4,5	0,078	0,079	0,565	0,745
5	0,062	0,098	0,615	0,782
5,5	0,05	0,127	0,659	0,813
6	0,04	0,163	0,694	0,836
6,5	0,033	0,202	0,725	0,855
7	0,025	0,248	0,763	0,878
7,5	0,021	0,304	0,78	0,889
8	0,015	0,368	0,816	0,909
8,5	0,012	0,418	0,836	0,92
9	0,009	0,512	0,856	0,93
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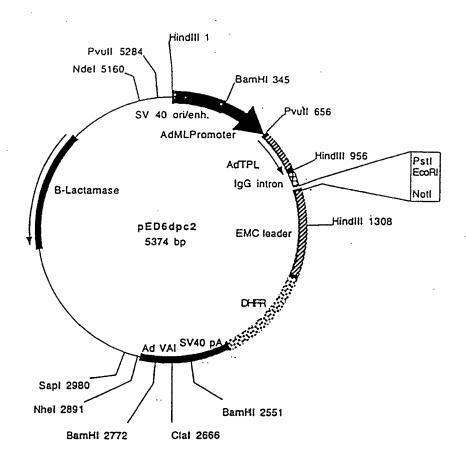
influence of minimum score on signal peptide recognition



Minimum signal peptide score	All ESTs	New ESTs	ESTs matching public EST closer than 40 bp from beginning	ESTs extending known mRNA more than 40 bp	ESTs extending public EST more than 40 bp
3,5	2674	947	599	23	150
4	2278	784	499	23	126
4,5	1943	647	425	22	112
5	1657	523	353	21	96
5,5	1417	419	307	19	80
6	1190	340	238	18	68
6,5	1035	280	186	18	60
7	893	219	161	15	48
7,5	753	173	132	12	36
8	636	133	101	11	29
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9	456	81	63	6	24
9,5	364	57	48	6	18
10	303	47	35	6	15

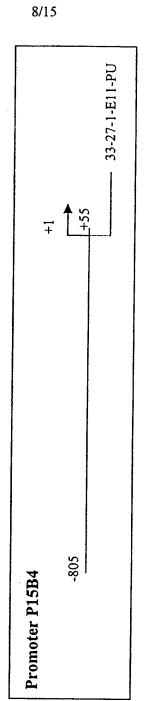
	····				
Tissue	All ESTs	New ESTs	ESTs matching public EST closer than 40 bp from beginning	ESTs extending known mRNA more than 40 bp	ESTs extending public EST more than 40 bp
Brain	329	131	75	. 3	24
Cancerous prostate	134	40	37	1	6
Cerebellum	17	. 9	1	0	6
Colon	21	11	4	0	0
Dystrophic muscle	41	18	8	0	1
Fetal brain	70	37	16	0	1
Fetal kidney	227	116	46	1	19
Fetal liver	13	7	2	0	o.
Heart	30	15	7	0	1
Hypertrophic prostate	86	23	22	2	2
Kidney	10	7	3	. 0	0
Large intestine	21	8	4	0	1
Liver	23	9	6	0	o
Lung	24	12	4	0	1
Lung (celis)	57	38	6	0	4
Lymph ganglia	163	60	23	2	12
Lymphocytes	23	6	4	0	2
Muscle	33	16	6	0	4
Normal prostate	181	61	45	7	11
Ovary	90	57	12	1	2
Pancreas	48	11	6	0	1
Placenta	24	5	1	0	o
Prostate	34	16	4	0	2
Spleen	56	28	10	0	1
Substantia nigra	108	47	27	1	6
Surrenals	15	3	3	.1	0
Testis	131	68	25	1	
Thyroid	17	8	2	0	2
Umbilical cord	55	17	12	1	8 2 3
Uterus	28	15	3	0	2
Non tissue-specific	568	48	177	2	28
Total	2677	947	601	23	150





Plasmid name: pED6dpc2 Plasmid size: 5374 bp

33-30-4-C4-PU Description of promoters structure isolated from SignalTag 5 'ESTs +29 7 -517 Promoter P13H2



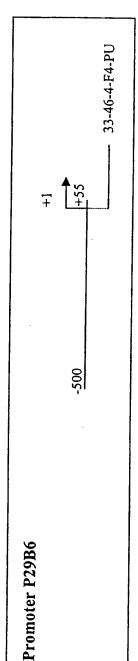


FIGURE 8

WO 99/31236 PCT/IB98/02122

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Description of Transcription Factor Binding Sites present on promoters isolated from SignalTag sequences

Promoter sequence P13H2 (546 bp):

Matrix	Position	Orientation	Score	Length	Sequence
CMYB_01	-502	+	0.983	9	TGTCAGTTG
MYOD_Q6	-501	·	0.961	10	CCCAACTGAC
S8_01	-444	-	0.960	11	AATAGAATTAG
S8_01	-425	+	0.966	11	AACTAAATTAG
DELTAEF1_01	-390	•	0.960	. 11	GCACACCTCAG
GATA_C	-364	-	0.964	11	AGATAAATCCA
CMYB_01	-349	+	0.958	9	CTTCAGTTG
GATA1_02	-343	+	0.959	14	TTGTAGATAGGACA
GATA_C	-339	+	0.953	11	AGATAGGACAT
TAL1ALPHAE47_01	-235	+	0.973	16	CATAACAGATGGTAAG
TAL1BETAE47_01	-235	+	0.983	16	CATAACAGATGGTAAG
TAL1BETAITF2_01	-235	+	0.978	16	CATAACAGATGGTAAG
MYOD_Q6	-232	•	0.954	10	ACCATCTGTT
GATA1_04	-217	•	0.953	13	TCAAGATAAAGTA
IK1_01	-126	+	0.963	13	AGTTGGGAATTCC
IK2_01	-126	+	0.985	12	AGTTGGGAATTC
CREL_01	-123	+	0.962	10	TGGGAATTCC
GATA1_02	-96	+	0.950	14	TCAGTGATATGGCA
SRY_02	-41	-	0.951	12	TAAAACAAAACA
E2F_02	-33	+	0.957	8	TTTAGCGC
MZF1_01	-5	•	0.975	8	TGAGGGGA

Promoter sequence P15B4 (861bp):

Matrix	Position	Orientation	Score	Length	Sequence
NFY_Q6	-748	•	0.956	11	GGACCAATCAT
MZF1_01	-738	+	0.962	8	CCTGGGGA
CMYB_01	-684	. +	0.994	9	TGACCGTTG
VMYB_02	-682	-	0.985	9	TCCAACGGT
STAT_01	-673	+	0.968	9	TTCCTGGAA
STAT_01	-673	-	0.951	9	TTCCAGGAA
MZF1_01	-556	-	0.956	8	TTGGGGGA
IK2_01	-451	+	0.965	12	GAATGGGATTTC
MZF1_01	-424	+	0.986	8	AGAGGGGA
SRY_02	-398	-	0.955	12	GAAAACAAAACA
MZF1_01	-216	+	0.960	8	GAAGGGGA
MYOD_Q6	-190	+	0.981	10	AGCATCTGCC
DELTAEF1_01	-176	+	0.958	11	TCCCACCTTCC
S8_01	5	-	0.992	11	GAGGCAATTAT
MZF1_01	16	-	0.986	8	AGAGGGGA

Promoter sequence P29B6 (555 bp):

Matrix	Position	Orientation	Score	Length	Sequence
ARNT_01	-311	+	0.964	16	GGACTCACGTGCTGCT
NMYC_01	-309	+	0.965	12	ACTCACGTGCTG
USF_01	-309	+	0.985	12	ACTCACGTGCTG
USF_01	-309	-	0.985	12	CAGCACGTGAGT
NMYC_01	-309	-	0.956	12	CAGCACGTGAGT
MYCMAX_02	-309	•	0.972	12	CAGCACGTGAGT
USF_C	-307	+	0.997	8	TCACGTGC
USF_C	-307	-	0.991	8	GCACGTGA
MZF1_01	-292	-	0.968	8	CATGGGGA
ELK1_02	-105	+	0.963	14	CTCTCCGGAAGCCT
CETS1P54_01	-102	+	0.974	10	TCCGGAAGCC
AP1_Q4	-42	-	0.963	11	AGTGACTGAAC
AP1FJ_Q2	-42	-	0.961	11	AGTGACTGAAC
PADS_C	45	+	1.000	9	TGTGGTCTC

Figure 9

100.0% identity in 125 aa overlap SEQ ID NO: 217 MADEELEALRRQRLAELQAKHGDPGDAAQQEAKHREAEMRNSILAQVLDQSARARLSNLA SEQ ID NO: 516 MADEELEALRRQRLAELQAKHGDPGDAAQQEAKHREAEMRNSILAQVLDQSARARLSNLA SEQ ID NO: 217 LVKPEKTKAVENYLIQMARYGQLSEKVSEQGLIEILKKVSQQTEKTTTVKFNRRKVMDSD SEQ ID NO: 516 LVKPEKTKAVENYLIQMARYGQLSEKVSEQGLIEILKKVSQQTEKTTTVKFNRRKVMDSD SEQ ID NO: 217 EDDDY ::::X SEQ ID NO: 516 EDDDY

CLUSTAL W(1.5) multiple sequence alignment

SEQ ID NO: SEQ ID NO: SEQ ID NO: SEQ ID NO:	232 174	MFCPLKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCIFKIDWTLSMGCVFQSTEDKCIFKIDWTLSMGCVFQSTEDKRIFKIDWTLSMGCVFQSTVDKCIFKIDWTLS ******** ** *********
SEQ ID NO: SEQ ID NO: SEQ ID NO: SEQ ID NO:	232 174	PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDNLCNDGSLLLQDVQDVE PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDNLCNDGSLLLQDVQEADQGTYICEIRL PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL ************************************
SEQ ID NO: SEQ ID NO: SEQ ID NO: SEQ ID NO:	232 174	KGESQVFKKAVVLHVLPEEPKGTQMLTKGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEEKGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAK
SEQ ID NO: SEQ ID NO: SEQ ID NO: SEQ ID NO:	232 174	IVFRYYHKLRMSAEYSQSWGHFQNRVNLVGDIFRNDGSIMLQGVRESDGGNYTCSIHLGN VTRRKHHCVREGSG
SEQ ID NO: SEQ ID NO: SEQ ID NO: SEQ ID NO:	232 174	LVFKKTIVLHVSPEEPRTLVTPAALRPLVLGGNQLVIIVGIVCATILLLPVLILIVKKTC
SEQ ID NO: SEQ ID NO: SEQ ID NO: SEQ ID NO:	232 174	GNKSSVNSTVLVKNTKKTNP

99.6	5% i	dent	city	in 225 aa	overlap					٠.
			•	10	20	30	40	50	60	
SEQ	ID	NO:	515	PTAVQKEEA	RQDVEALLSR'	TVRTQILTG	KELRVATQE	KEGSSGRCMI	TLLGLSFILA	AGLI
							::::::	::::::::		::::
SEQ	ID	NO:	231				LRVATQE	KEGSSGRCMI		
								10	20	30
				70	80	90	100	110	120	
SEO.	TD	NO.	515	. •	FMPKSTIYRG					עמדז
SEQ	ים	140.	213	VOGACIIKI	·····		······		DIREDUNIA	
SEO	TD	NO:	231	VGGACTYKY	FMPKSTIYRG	EMCFFDSED	PANSLEGGE	PNFLPVTEEA	DIREDDNIA	IDV
224				4			60	70	80	90
									-	
			:	130	140	150	160	170	180	
SEQ	ID	NO:	515	PVPSFSDSD	PAAIIHDFEK	GMTAYLDLL	LGNCYLMPL	NTSIVMPPKN	ILVELFGKLAS	SGRY
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SEQ	ID	NO:	231	PVPSFSDSD	PAAIIHDFEK	GMTAYLDLL	LGICYLMPL	NTSIVMPPKN	ILVELFGKLAS	GRY
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				•		210	220	230	240	
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CEO	TD	NO.	221		:::::::: DLVAVEEIRD					
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				10	1,		00		200	210
				250	260					
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-					:::::					
SEQ	ID	NO:	231	HFPNEFIVE	TKICQE					

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SEQ ID NO:158 PP

Bod tablet attack seekke tikk en of de beken tie of the boune of the development entry. I takk hen yeek was broken at the boune of the

14/15

98.5% identity in 194 aa overlap SEQ ID NO:519 ARNLPPLTDAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVRQLEDLVIEAVYADVL SEQ ID NO:158 ARNLPPLTEAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVRQLEDLVIEAVYADVL SEQ ID NO:519 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIAQTLQEWCVGCEVVLSGIEEQVSRANQHKEQ SEQ ID NO:158 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIARTLQEWCVGCEVVLSGIEEQVSRANQHKEQ SEQ ID NO:519 QLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQHLTELREPASGTNQRQPSKKASKG SEQ ID NO:158 QLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQHLTELREPAPGTNQRQPSKKASKG SEQ ID NO:519 KGLRGSAKIWSKSN SEQ ID NO:158 KGLRGSAKIWSKSN 88.7% identity in 62 aa overlap SEQ ID NO:519 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELAESDF SEQ ID NO:158 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELXARNL SEQ ID NO:519 AS

68.9% identity in 74 aa overlap

SEQ ID NO:514 QLLYITSFVFVGYYLLKRQDYMYAVRDHDMFSYIKSHPEDFPEKDKKTYGEVFEEFHPVR
70 80 90 100 110 120

. WO 99/31236 PCT/IB98/02122

Karabahandan dinadanan cerebir indira karabahan dinada keli daribahan kananda dan keli daribahan kengan dan dinada dan kelimbah dan berana dan dinada dan

<110> Dumas Milne Edwards, Jean-Baptiste Duclert, Aymeric Bougueleret, Lydie

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Glu Arg Glu Lys Arg Ser Ile Ser Asp Ser Asp Glu Leu Ala Ser Gly
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                                          35
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                                       50
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                                                                   354
Pro Glu Ser Ala Pro Thr Thr Pro Leu Pro Ser Glu Lys
               60
                                   65
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aagactaaca ttttgtgaag ttgtaaaaca gaaaacctgt tagaa atg tgg tgt tt Met Trp Trp Phe	55.
-20	
cag caa ggc ctc agt ttc ctt cct tca gcc ctt gta att tgg aca tct	405
Gln Gln Gly Leu Ser Phe Leu Pro Ser Ala Leu Val Ile Trp Thr Ser	
-15 -10 -5	
get get tte ata ttt tea tae att act gea gta aca ete cae cat ata	453
Ala Ala Phe Ile Phe Ser Tyr Ile Thr Ala Val Thr Leu His His Ile	
1 5 10 15	
gac ccg gct tta cct tat atc agt gac act ggt aca gta gct cca raa	501
Asp Pro Ala Leu Pro Tyr Ile Ser Asp Thr Gly Thr Val Ala Pro Xaa	
20 25 30	
aaa tgc tta ttt ggg gca atg cta aat att gcg gca gtt tta tgt caa	549
Lys Cys Leu Phe Gly Ala Met Leu Asn Ile Ala Ala Val Leu Cys Gln	
35 40 45	
aaa tagaaatcag gaarataatt caacttaaag aakttcattt catgaccaaa	602
Lys	.=
ctcttcaraa acatgtcttt acaagcatat ctcttgtatt gctttctaca ctgttgaatt	662

405

gtctggcaat atttctgcag tggaaaattt gatttarmta gttcttgact gataaatatg 722 gtaaggtggg cttttccccc tgtgtaattg gctactatgt cttactgagc caagttgtaw 782 822 " <210> 20 <211> 21 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> 1..21 <223> Von Heijne matrix score 5.5 seq SFLPSALVIWTSA/AF <400> 20 Met Trp Trp Phe Gln Gln Gly Leu Ser Phe Leu Pro Ser Ala Leu Val 10 Ile Trp Thr Ser Ala 20 <210> 21 <211> 405 <212> DNA <213> Homo sapiens <220> <221> misc feature <222> complement (103..398) <223> blastn <221> sig_peptide <222> 185..295 <223> Von Heijne matrix <400> 21 atcaccttct tctccatcct tstctgggcc agtccccarc ccagtccctc tcctgacctg 60 cccagcccaa gtcagccttc agcacgcgct tttctgcaca cagatattcc aggcctacct 120 ggcattccag gacctccgma atgatgctcc agtcccttac aagcgcttcc tggatgaggg 180 tggc atg gtg ctg acc acc ctc ccc ttg ccc tct gcc aac agc cct gtg 229 Met Val Leu Thr Thr Leu Pro Leu Pro Ser Ala Asn Ser Pro Val -35 -30 aac atg ecc acc act gge ecc aac age etg agt tat get age tet gee 277 Asn Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala -20 -15 ctg tcc ccc tgt ctg acc gct cca aak tcc ccc cgg ctt gct atg atg 325 Leu Ser Pro Cys Leu Thr Ala Pro Xaa Ser Pro Arg Leu Ala Met Met

5

1

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Pro Asp Asn

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Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala Leu
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Ser Pro Cys Leu Thr
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 cccggagata ggaccaaccg tcaggaatgc gaggaatgtt tttcttcgga ctctatcgag
                                                                       180
 gcacacagac agacc atg ggg att ctg tct aca gtg aca gcc tta aca ttt
                                                                       231
                  Met Gly Ile Leu Ser Thr Val Thr Ala Leu Thr Phe
                                       -10
                  -15
 gcc ara gcc ctg gac ggc tgc aga aat ggc att gcc cac cct gca agt
                                                                       279
 Ala Xaa Ala Leu Asp Gly Cys Arg Asn Gly Ile Ala His Pro Ala Ser
                             5
 gag aag cac aga ctc gag aaa tgt agg gaa ctc gag asc asc cac tcg
                                                                       327
 Glu Lys His Arg Leu Glu Lys Cys Arg Glu Leu Glu Xaa Xaa His Ser
                         20
 gcc cca gga tca acc cas cac cga aga aaa aca acc aga aga aat tat
                                                                       375
 Ala Pro Gly Ser Thr Xaa His Arg Arg Lys Thr Thr Arg Arg Asn Tyr
                                                              45
                                          40
                     35
                                                                        424
 tct tca gcc tgaaatgaak ccgggatcaa atggttgctg atcaragccc
 atatttaaat tggaaaagtc aaattgasca ttattaaata aagcttgttt aatatgtctc
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                                                                        496
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                                                                      105
Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala Ser Ala Gly
                                 -5
            -10
                                                                      153
tgc gcc acg acg cca gct cgc aac ctg agc tgc tac cag tgc ttc aag
Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln Cys Phe Lys
                        10
gtc agc agc tgg acg gag tgc ccg ccc acc tgg tgc agc ccg ctg gac
                                                                      201
Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser Pro Leu Asp
                                                             35
                    25
                                                                      249
caa gtc tgc atc tcc aac gag gtg gtc gtc tct ttt aaa tgg agt gta
Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Lys Trp Ser Val
                40
                                    45
                                                                      297
cgc gtc ctg ctc agc aaa cgc tgt gct ccc aga tgt ccc aac gac aac
Arg Val Leu Leu Ser Lys Arg Cys Ala Pro Arg Cys Pro Asn Asp Asn
                                60
            55
atg aak ttc gaa tgg tcg ccg gcc ccc atg gtg caa ggc gtg atc acc
                                                                       345
Met Xaa Phe Glu Trp Ser Pro Ala Pro Met Val Gln Gly Val Ile Thr
                                                 80
                                                                       393
agg ege tge tgt tee tgg get ete tge aac agg gea etg ace eea cag
Arg Arg Cys Cys Ser Trp Ala Leu Cys Asn Arg Ala Leu Thr Pro Gln
    85
                                             95
                        90
gag ggg cgc tgg gcc ctg cra ggg ggg ctc ctg ctc cag gac cct tcg
Glu Gly Arg Trp Ala Leu Xaa Gly Gly Leu Leu Gln Asp Pro Ser
                    105
agg ggc ara aaa acc tgg gtg cgg cca cag ctg ggg ctc cca ctc tgc
                                                                       489
Arg Gly Xaa Lys Thr Trp Val Arg Pro Gln Leu Gly Leu Pro Leu Cys
                120
                                     125
ctt ccc awt tcc aac ccc ctc tgc cca rgg gaa acc cag gaa gga
                                                                       534
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Asp Gln Thr Leu Glu Phe Leu Lys Ile Pro Ser Thr Leu Ala Pro Pro

	-
•••	
110 115 120	
atg gac cca tct gtg ccc atc tgg att att ata ttt ggt gtg ata ttt	484
Met Asp Pro Ser Val Pro Ile Trp Ile Ile Ile Phe Gly Val Ile Phe	••
125 130 135	
tgc atc atc ata gtt gca att gca cta ctg att tta tca ggg atc tgg	532
Cys Ile Ile Val Ala Ile Ala Leu Leu Ile Leu Ser Gly Ile Trp	
215 150	
caa cgt ada ara aag aac aaa gaa cca tct gaa gtg gat gac gct gaa	580
Gln Arg Xaa Xaa Lys Asn Lys Glu Pro Ser Glu Val Asp Asp Ala Glu 155 160 165	
rat aak tgt gaa aac atg atc aca att gaa aat ggc atc ccc tct gat	
Xaa Xaa Cys Glu Asn Met Ile Thr Ile Glu Asn Gly Ile Pro Ser Asp	628
170	
175 180 185 ccc ctg gac atg aag ggg ggg cat att aat gat gcc ttc atg aca gag	
Pro Leu Asp Met Lys Gly Gly His Ile Asn Asp Ala Phe Met Thr Glu	676
4.44	
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Asp Glu Arg Leu Thr Pro Leu	727
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المقار الشاعفي والاستناف المناف المتما وليتك والرازان والمتعاوية والمعتقدة والمتعالمة والمعتقب والمتعارب والمتعاور و

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 score 0.961
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- <222> 618..627
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                                                                120
180
ctcagagggc taggcacgag ggaaggtcag aggagaaggs aggsarggcc cagtgagarg
                                                                240
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                                                                300
aaytcagggc ccaascagaa scacaggccc aktcntggct smaagcacaa tagcctgaat
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sequence gcacgtga

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gcc ctc ctc ctg cct cac tgc cag aag ccc ttt gtg tat gac ctt cac Ala Leu Leu Leu Pro His Cys Gln Lys Pro Phe Val Tyr Asp Leu His 1 5 10 15	144
gca gtc aag aac gac ttc cag att tgg agg ttg ata tgt gga aga ata Ala Val Lys Asn Asp Phe Gln Ile Trp Arg Leu Ile Cys Gly Arg Ile 20 25 30	192
att tgc ctt gat ttg aaa gat act ttc tgc agt agt ctg ctt att tat Ile Cys Leu Asp Leu Lys Asp Thr Phe Cys Ser Ser Leu Leu Ile Tyr 35 40 45	240
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ttt Phe	Leu	ctg Leu	ggt Gly	acc Thr	tgg Trp	Val	ttg Leu	tca Ser	gcc Ala	tta Leu	ttt Phe	gac Asp	ttt Phe	ctc Leu	ctc Leu	336
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Pro	Ser	Glv	Len	Tle	Phe	Cve	Cve	272	Dhe	Cyc	200	Clu	The	Lys	Ton	734
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Pne	ren	ser		Gin	Ala	Met	Ala	Glu	Asn	Phe	Ser	Ile				
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Asn	Arg	Asp	Trp	Tyr	Lys	Arg	Asn	Phe	Ala	Ile	Thr	Phe	Phe	Met	Gly	
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Lvs	Val	Ala	T.en	Glu	Ara	Tle	Trn	λαπ	Lare	Lou	Tuo	Cl-	T	Gln	449 *	320
					**** 9	110	тър			neu	ոչո	GIII	nys		гÀв	
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Lys	Arg	Ser	Asn													
			55													
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agee		J- 6 a+ ~	+	+	~ ~~	-uca	2223		-yay	uaa	aaut	yyag	ee g	JALCE	caaga	432
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actg	-999	cc g	cctg	cctg	c tg	atgt	gggc	tct	aggc	cag	cttg	ttgt	ca c	gtac	gtggt	552
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            -15
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Gly Ala Ala Phe Tyr Pro Ile Tyr Phe Arg Pro Leu Met Arg Leu Glu
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Glu Tyr Lys Lys Glu Gln Ala Ile Asn Arg Ala Gly Ile Val Gln Glu
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Asp Val Gln Pro Pro Gly Leu Lys Val Trp Ser Asp Pro Phe Gly Arg
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T.en	Glu	Δla	T.em	Ara	Asp	Tle	Leu	His	Asp	Ile	Thr	Pro	Asn	Val	Leu	
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AIa		Ser	GIY	Val	ъси	135			· IIDp	***	140					
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2++	2	2020	2-30	+	oct t		ישפהי	יים אל דר הי	rtast	-222	,	taci	taat	tttt	gcagctt	1960
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Thr Asp Gly Leu Ala Ala Ile Asn Leu Leu Lys Trp Ile Lys Thr Leu
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 Gly Gly Ser Val Ile Ser Met Ile Val Leu Leu Ile Cys Val Val Cys
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 Leu Tyr Ile Val Cys Arg Cys Gly Ser His Leu Trp Arg Glu Ser His
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 cac tgagagcaag caatgatagc tgtggcggtt ttgcaaaaag aaaagggaga
 His
 10
                                                                       729
 caagegeeca getatagtta ccaataaage atggtaetgg tattaaaata ggeatgtgtt
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                         100
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 110
                                                                       583
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135

130

WO 99/31236

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gac	atg	ccc	aat	gtt	aga	gag	ctg	naa	gcc	cgg	aat	ctt	CCC	cca	Cta	312
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	~~~	~~+	-35 cag	224	22+	224	ctt	-30	cac	ctc	tra	att		acc	cta	360
aca	gag	31a	Gln	Lve	Adu	Tare	Len	Ara	His	Len	Ser	Val	Val	Thr	Leu	• • •
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гÀг	Gln	inr	ьys			Pne	TIE									
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Ile	e Val	l Gli	a Ala	a Cys	Lys	: Ala	Ly	s Thr	Ası) Ala	ניטו	/ Giy	GIU	. wah	135	
121	`				125	5				130	,				133	680
ati	t tt	g caa	acc	c aga	act	tat	: ga	c ctt	: ta	ato	: act	tat	. gat	. aad	Lat	
-	•	_														

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Pro Leu Thr Val Glu His Met Tyr Glu Asp Ile Ser Gln Asp His Val	
and and acc att gam and cat cot cat ctg cca cca cct ccc	824
Lys Lys Thr Val Thr Ile Glu Asn His Pro His Leu Pro Pro Pro	
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Met Cys Ser Val His Pro Cys Arg His Ala Glu Val Met Lys Lys Ile	
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Leu Leu Ile Phe Leu Lys Phe Val Gln Ala Val Ile Pro Thr Ile Glu 235 240 245	
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cgc aga ccc aga ctt ggc cgt tgc tct gac atg gac aca gcc agg aca Arg Arg Pro Arg Leu Gly Arg Cys Ser Asp Met Asp Thr Ala Arg Thr -60 -55 -50	755
age tge tca gac ctg ctt ccc tgg gag ggg gtg acg gaa cca gca ctg Ser Cys Ser Asp Leu Leu Pro Trp Glu Gly Val Thr Glu Pro Ala Leu -45	803
tgt gga gac cag ctt caa gga acg gaa ggc tgg ctt gag gcc aca cag Cys Gly Asp Gln Leu Gln Gly Thr Glu Gly Trp Leu Glu Ala Thr Gln -30 -25 -20	851
ctg ggg cgg gga ctt ctg tct gcc tgt gct cca tgg ggg gac ggc tcc Leu Gly Arg Gly Leu Leu Ser Ala Cys Ala Pro Trp Gly Asp Gly Ser -15 -10 -5	899
acc cag cct gtg cca ctg tgt tct taagaggett ccagagaaaa cggcacacca Thr Gln Pro Val Pro Leu Cys Ser	953
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atg aag agt cgg gag cag gga gga cgg ctg gga gcc gaa agc cgg acc Met Lys Ser Arg Glu Gln Gly Gly Arg Leu Gly Ala Glu Ser Arg Thr 15 20 25	146
ctg ctg gtc ata gcg cac cct gac gat gaa gcc atg ttt ttt gct ccc Leu Leu Val Ile Ala His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro 30 35 40	194
aca gtg cta ggc ttg gcc cgc cta agg cac tgg gtg tac ctg ctt tgc Thr Val Leu Gly Leu Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys 50 50 60	242
ttc tct gca gtt ttc cgt agg gag cta agt gaa tac acc gaa ggt ctt Phe Ser Ala Val Phe Arg Arg Glu Leu Ser Glu Tyr Thr Glu Gly Leu 65 70	290
ace tet gaa eee ete aca gee tagggacagg ageggeegge ttacetggtg Thr Ser Glu Pro Leu Thr Ala 80	341
ggttggggga cgtcggcagc tcgcgtacta cgccagcagg attgaggagc agagaaacag	401

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461

521

568

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catg	gctt	ca g	cgtc	tgct	c gt	ggaa	acca	aga	itaaa	gat	gccc	attt	tc c	acca	ccaag	174
caage	cagc	tc t	.gcct	tttt	c to	ttgt	aago	: atg Met	: Let	val	Thr	Gli	1 Gl)	Let -30	ı Val	1/4
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tac Tyr	caa Gln	ggt Gly	Tyr	Leu	Ala	Ala	Asn	Ser	Arg	Phe	Gly	Ser	Leu	Pro	Lys	
			-25					-20					-15			220
gtt	gca	ctt	gct	ggt	ctc	ttg	gga	ttt	ggc	ctt	gga	aag	gta	tca	tac	270
Val .	Ala	Leu -10	Ala	Gly	Leu	Leu	Gly	Phe	Gly	Leu	Gly	Lys 1	Val	ser	Tyr	
ata	aas	gta	tac	саσ	agt	aaa	ttc	cat	ttt	ttt	gaa	gat	cag	ctc	cgt	318
Ile	Glv	Val	Cvs	Gln	Ser	Lys	Phe	His	Phe	Phe	Glu	Asp	Gln	Leu	Arg	
5	,		-1-		10	•				15					20	
aaa	act	aat	ttt	aat	cca	cag	cat	aac	agg	cac	tgc	ctc	ctt	acc	tgt	366
Gly	Ala	Gly	Phe	Gly 25	Pro	Gln	His	Asn	Arg 30	His	Сув	Leu	Leu	Thr	Сув	
gag	~ 22	tac	222		aad	cat	gga	tta		gag	aaq	qqa	qac	tct	cag	414
Glu	gaa Glu	Cyc	Lvc	Tle	LVS	His	Glv	Leu	Ser	Glu	Lys	Gly	Asp	Ser	Gln	
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Pro	Ser	Ala 55	Ser													
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                                              235
cag tee tte ege ate ace ate ett eeg cag caa tae etg egg eea gtg
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Gln Ser Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr Leu Arg Pro Val
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Glu Asp Val Ala Thr Ser Gln Asp Asp Cys Tyr Lys Phe Ala Ile Ser
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                   260
cag tca tcc acg ggc act gtt atg gga gct gtt atc atg gag ggc ttc
                                                                    915
Gln Ser Ser Thr Gly Thr Val Met Gly Ala Val Ile Met Glu Gly Phe
                                   280
               275
                                                                    963
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Tyr Val Val Phe Asp Arg Ala Arg Lys Arg Ile Gly Phe Ala Val Ser
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get tge cat gtg cae gat gag tte agg aeg gea geg gtg gaa gge een
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Ala Cys His Val His Asp Glu Phe Arg Thr Ala Ala Val Glu Gly Pro
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                                                                   1059
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Phe Cys His Leu Gly His Gly Arg Leu Trp Leu Gln His Ser Thr Asp
                       325
                                                                   1112
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Arg
335
tetteatget gecaetetge etcatggtgt gteagtggeg etgeeteege tgeetgegee
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cgggaaattc tgctgcttga aacttcagcc ctgaaccttt gtcaccattc ctttaaattc
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                                                                   1652
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<221> polyA_site

<222> 1673..1686

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agc ggg att gat ctc ctt ag	gg acc tat ctt tgg	cgt tgc cag ttc ctt .	158
Ser Gly Ile Asp Leu Leu A			
	30	-25	
tta cct ttt gtg agt tta gg			206
Leu Pro Phe Val Ser Leu G			
-20 -15	-10	-5	254
ctt tgt gct tgc att tgc cg Leu Cys Ala Cys Ile Cys An			254
ned cys Ara cys fie cys Ar	rg ser bed lyr Pro	10	÷
att ctc cat ctc ctt gca g	at cta tat aca cta	- -	302
Ile Leu His Leu Leu Ala G			
15	20	25	
tat gtt gct gga att gaa c	ta ctc cac cag aaa	cta gag ctc cct gac	350
Tyr Val Ala Gly Ile Glu Le	eu Leu His Gln Lys	Leu Glu Leu Pro Asp	
30 3!		40	
aat gta too ggt gaa ttt g			398
Asn Val Ser Gly Glu Phe G	-		
45 50	55	60	
gct ccc tta cag ttc atg gc			446
Ala Pro Leu Gln Phe Met A	ia ser Ala Leu Phe 70	75	
acc aac cgg aga gag tac a	· -	· -	491
Thr Asn Arg Arg Glu Tyr T			471
80	85	90	
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ttttccccac ctctcaattg ttt	_	-	611
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aatggataga gacttgacac aaa			791
aacaagttgt gctaatgtct gtt			851
aactaaaaac tctatattag ttt			911
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aatacagtgt ttacttgaaa ttt			1151
gaggattagt attattttta act			1211
ttttttttt ttcctcttca cat			1271
tattacagtt acaaggtaaa att			1331
aaagaacgtt tcaccataat gac			1391
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.ttccttgcct aaatcccttc ctg		-	1511
catttttat aagtatgtct ata	-		1571
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tgc cgg aag tac tac ctg ggg ggg ttt gct ttc ttg cct ttt ctc tgg Cys Arg Lys Tyr Tyr Leu Gly Gly Phe Ala Phe Leu Pro Phe Leu Trp -50 -45	158
ttg gtc aac atc ttc tgg ttc tac cga gag gcc ttc ctt gtc cca gcc Leu Val Asn Ile Phe Trp Phe Tyr Arg Glu Ala Phe Leu Val Pro Ala -40 -35 -30	206
tac aca gaa cag agc caa atc aaa ggc tat gtc tgg cgc tca gct gtg Tyr Thr Glu Gln Ser Gln Ile Lys Gly Tyr Val Trp Arg Ser Ala Val	254
ggc ttc ctc ttc tgg gtg ata gtg ctc acc tcc tgg atc acc atc ttc Gly Phe Leu Phe Trp Val Ile Val Leu Thr Ser Trp Ile Thr Ile Phe	302
cag atc tac egg ecc ege tgg ggt gec ett ggg gae tac etc tec tte Gln Ile Tyr Arg Pro Arg Trp Gly Ala Leu Gly Asp Tyr Leu Ser Phe	350
10 15 20 acc ata ccc ctg ggc acc ccc tgacaacttc tgcacatact ggggccctgc Thr Ile Pro Leu Gly Thr Pro	401
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-50 -45 -40 age ege aac ect gag gtg eec ttt gag age agt gee tae ege ate tea	145

Ser	Arg	Asn	.Pro	Glu	Val	Pro	Phe	Glu	Ser	Ser	Ala -25	Tyr	Arg	Ile	Ser			
Ala -20	tca Ser	gcc Ala	Arg	Gly	Lys -15	gag Glu	Leu	Arg	Leu	Ile	Leu	Ser	Pro	Leu	Pro -5	193		
Gly 999	gcc Ala	cag Gln	cct Pro	caa Gln 1	cag Gln	gag Glu	cca Pro	ctg Leu 5	gcc Ala	ctg Leu	gtc Val	ttc Phe	cgc Arg 10	ttc Phe	ggc Gly	241		
		ggc Gly 15														289		
gcc Ala	cac His 30	ctg Leu	cgc Arg	ttt Phe	tac Tyr	acg Thr 35	gcc Ala	ccg Pro	cct Pro	ggc Gly	ccc Pro 40	cgg Arg	ctc Leu	gcc Ala	cta Leu	337		
		gtg Val														385		
tgg Trp	cag Gln	ccg Pro	ggc Gly	cgc Arg 65	G1y 999	ccc Pro	tgt Cys	gtc Val	ttg Leu 70	cag Gln	gag Glu	tac Tyr	cag Gln	cag Gln 75	ttc Phe	433		
		aat Asn														481		
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		cgc Arg														625		
		acc Thr														673		
ctg Leu	ctg Leu	gag Glu	cta Leu 160	tgt Cys	cac His	tca Ser	gtg Val	ccc Pro 165	aag Lys	gaa Glu	gtg Val	gtc Val	cag Gln 170	ttg Leu	ggt Gly	721		
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acc	ctqa	ggc	actt	gtcc	cc c	tcta	gacc	t ga	ttca	ccga	ttt	ggaa	gtt	tgta	gcccta	827		
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WO 99/31236

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•	
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Asp Ala Leu Pro Pro Ser Lys Ala Pro Ser Lys Thr Arg Arg Ala Lys	
205 210 215 220	913
aga gac ctt cct aag agg act gca acc cag cgg cct gag ggg acc agc Arg Asp Leu Pro Lys Arg Thr Ala Thr Gln Arg Pro Glu Gly Thr Ser	213
225 230 235	
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Ala Asp Ile Pro Ser Leu Glu Pro Glu Gly Thr Ser Ala Ser	
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15 20 25	

pida Mar

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gy (n

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        Met Ala Ser Pro Ala Val Asn Arg Trp Lys Arg Pro Arg Leu
                                                         -25
                                     -30
                -35
                                                                       97
aag ccg gtg tgg cca cgg cgc ttg gaa tcc tgg ttg ttg ctg gat gct
Lys Pro Val Trp Pro Arg Arg Leu Glu Ser Trp Leu Leu Leu Asp Ala
                                -15
            -20
ctt ttg cga tta gga gat acc aaa aaa aag cga cag cct gaa gca gcc
                                                                      145
Leu Leu Arg Leu Gly Asp Thr Lys Lys Lys Arg Gln Pro Glu Ala Ala
                            1
        -5
                                                                       193
aca aaa too tgt gtt aga ago ago tgt ggg ggt coc agt gga gat ggg
Thr Lys Ser Cys Val Arg Ser Ser Cys Gly Gly Pro Ser Gly Asp Gly
                                        20
                    15
cct ccc cca tgc ctc cag cag cct gac cct cgt gcc ctg tct cag gcg
                                                                       241
Pro Pro Pro Cys Leu Gln Gln Pro Asp Pro Arg Ala Leu Ser Gln Ala
                30
ttc tct aga tcc ttt cct ctg ttt ccc tct ctc gct ggc aaa agt atg
                                                                       289
Phe Ser Arg Ser Phe Pro Leu Phe Pro Ser Leu Ala Gly Lys Ser Met
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                                                                       342
atc taattgaaac aagactgaag gatcaataaa cagccatctg ccccttcaaa
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aaaaaaaaa
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<222> 16..84

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<221> polyA signal

<222> 502..507

<221> polyA_site

<222> 522..542

では、日本の主義を持ちては、日本の主義を持ち

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-20 -15 ctc ttc ttc ttt ctc ttc ctc ctc acc agg ggc tca ctt tct cca acc Leu Phe Phe Phe Leu Phe Leu Leu Thr Arg Gly Ser Leu Ser Pro Thr -10 -5 1 5	a 99
aaa tat aac ctt ttg gag ctc aag gag tct tgc atc cgg aac cag gad Lys Tyr Asn Leu Leu Glu Leu Lys Glu Ser Cys Ile Arg Asn Gln Asj 10 15 20	2 147
tgc gag act ggc tgc tgc caa cgt gct cca gac aat tgc gag tcg cac Cys Glu Thr Gly Cys Cys Gln Arg Ala Pro Asp Asn Cys Glu Ser His 25 30 35	c 195 s
tgc gcg gag aag ggg tcc gag ggc agt ctg tgt caa acg cag gtg ttc Cys Ala Glu Lys Gly Ser Glu Gly Ser Leu Cys Gln Thr Gln Val Pho 40 45 50	c 243 e
ttt ggc caa tat aga gcg tgt ccc tgc ctg cgg aac ctg act tgt atc Phe Gly Gln Tyr Arg Ala Cys Pro Cys Leu Arg Asn Leu Thr Cys Il 55 60 65	a 291 e
tat tca aag aat gag aaa tgg ctt agc atc gcc tat ggc cgt tgt ca Tyr Ser Lys Asn Glu Lys Trp Leu Ser Ile Ala Tyr Gly Arg Cys Gl 70 75 80 85	n
aaa att gga agg cag aag ttg gct aag aaa atg ttc ttc tagtgctccc Lys Ile Gly Arg Gln Lys Leu Ala Lys Lys Met Phe Phe 90 95	
tccttcttgc tgcctcctcc tcctccacct gctctcctcc ctacccagag ctctgtg accctgttcc ccagagcctc caccatgagt ggagggaagt ggggagtgat tgaaata agctttttca atgaaaaaaa aaaaaaaaa aaaa	ttc 448 aag 508 542
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att caa gta ttg aag atg ctg cca agg gaa aaa tta aga aga aga ga Ile Gln Val Leu Lys Met Leu Pro Arg Glu Lys Leu Arg Arg Arg Gl 20 25 30	
gag aga aaa caa ata aat ggg aaa aaa gaa agg aca aaa tat gaa ac Glu Arg Lys Gln Ile Asn Gly Lys Lys Glu Arg Thr Lys Tyr Glu Th	a 203
cca aga aaa aga gaa gga aaa aaa aaa Pro Arg Lys Arg Glu Gly Lys Lys Lys 50 55	233

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                         Met Val Ala Leu Asn Leu Ile Leu Val Pro
                                         -10
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                                                                      160
Cys Cys Ala Ala Trp Cys Asp Pro Arg Arg Ile His Ser Gln Asp Asp
                                                                      208
gtg ccc cgt agc tct gct gct gat act ggg tct gcg atg cag cgg cgt
Val Pro Arg Ser Ser Ala Ala Asp Thr Gly Ser Ala Met Gln Arg Arg
                            20
gag gcc tgg gct ggt tgg aga agg tca caa ccc ttc tct gtt ggt ctg
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Glu Ala Trp Ala Gly Trp Arg Arg Ser Gln Pro Phe Ser Val Gly Leu
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                                                                      304
cct tct gct gaa aga ctc gag aac caa cca ggg aag ctg tcc tgg agg
Pro Ser Ala Glu Arg Leu Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg
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                    50
                                                                      350
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Ser Leu Val Gly Glu Gly Tyr Arg Ile Cys Asp Leu
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                                                                      410
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tgtctgtctg aggtgactta aaaaatcaga acaaaacttc tattatccag agtcatggga
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gagtacaccc tttccaggaa taatgttttg ggaaacactg aaatgaaatc ttcccagtat
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ctc	tgc	tta	ccc	aga	ccc	gaa	gca.	cgt	gag	gat	ccg	atc	cca	gtt	cct	1	.03
Leu	Cys	Leu	Pro	Arg	Pro	Glu	Ala	Arg	Glu		Pro	Ile	Pro	Val	Pro		
-55					-50					-45					-40	_	
сса	agg	ggc	ctg	ggt	gct	999	gag	999	tca	ggt	agt	cca	gtg	cgt	cca	1	51
Pro	Arg	Gly	Leu		Ala	Gly	Glu	Gly	Ser	Gly	Ser	Pro	Val	Arg	Pro		
				-35					-30					-25		-	00
cct	gta	tcc	acc	tgg	ggc	cct	agc	tgg	gcc	cag	ctc	ctg	gac	agt	gtc	1	99
Pro	Val	Ser		Trp	Glŷ	Pro	Ser		Ala	Gln	Leu	Leu		ser	vai		
			-20					-15					-10			-	247
cta	tgg	ctg	999	gca	cta	gga	ctg	aca	atc	cag	gca	gtc	דננ	tcc	acc	4	.4/
Leu	Trp		Gly	Ala	Leu	Gly		Thr	Ile	Gin		Val	Phe	ser	Thr		
•		-5					1				5					_	005
act	ggc	cca	gcc	ctg	ctg	ctg	ctt	ctg	gtc	agc	ttc	ctc	acc	דננ	gac		295
	Gly	Pro	Ala	Leu		Leu	Leu	Leu	Val		Phe	Leu	Thr	Phe	Asp		
10					15					20					25	-	
ctg	ctc	cat	agg	CCC	gca	ggt	cac	act	ctg	cca	cag	cgc	aaa	ctt	CTC	3	343
Leu	Leu	His	Arg		Ala	Gly	His	Thr	Leu	Pro	GIn	Arg	гуѕ	Leu	ьeu		
				30					35					40		-	0.01
acc	agg	ggc	cag	agt	cag	999	gcc	ggt	gaa	ggt	cct	gga	cag	cag	gag	-	391
Thr	Arg	Gly		Ser	Gln	Gly	Ala		Glu	Gly	Pro	GIA		Gin	GIU		
			45					50					55				
gct	cta	ctc	ctg	caa	atg	ggt	aca	gtc	tca	gga	caa	ctt	agc	CEC	cag	4	139
Ala	Leu		Leu	Gln	Met	Gly		Val	Ser	GIY			ser	Leu	GIN		
		60					65					70					187
gac	gca	ctg	ctg	ctg	ctg	ctc	atg	999	ctg	ggc	ccg	ctc	ctg	aga	gcc	•	10/
Asp		Leu	Leu	Leu	Leu		Met	Gly	Leu	GIY		Leu	Leu	Arg	Ата		
	75					80					85						535
tgt	ggc	atg	CCC	ttg	acc	ctg	ctt	ggc	ctg	gct	ttc	tgc	CCC	cat	CCT		222
	Gly	Met	Pro	Leu		Leu	Leu	GIA	Leu			Cys	Leu	HIS	Pro 105		
90					95					100							591
			gagc	ccc	tccc	caca	ac t	cagt	gtcc	t tc	aaat	atac	aat	yacc	acc	:	J J L
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att Ile -15	gag Glu	ctg Leu	gaa Glu	cct Pro	ggg Gly -10	ctg Leu	agc Ser	tcc Ser	agt Ser	gct Ala -5	gcc Ala	tgt Cys	aat Asn	G1 y 999	aag Lys 1	153
gag Glu	atg Met	tca Ser	cca Pro 5	acc Thr	agg Arg	caa Gln	ctc Leu	cgg Arg 10	agg Arg	tgc Cys	cct Pro	gga Gly	agt Ser 15	cat His	tgc Cys	201
ctg Leu	aca Thr	ata Ile 20	act Thr	gat Asp	gtt Val	ccc Pro	gtc Val 25	act Thr	gtt Val	tat Tyr	gca Ala	aca Thr 30	acg Thr	aga Arg	aag Lys	249
		gca					gaa Glu					tago	cacca	att		295
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)> 83 L> 43										•					
	2 > Dì				•											
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		ig_p		le .												
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\ 22.		core	•	- mai	LIIX											
	S	eq V	LVLC	VLLL(QAQG,	/GY										
	_	olyA 97		nal												
		olyA 21		ė												
	0 > 8															
gct	cacg	ctc	tggt	caga	gt t									gtc Val		51
														gac Asp		99
atg	agg Arg	atg Met	cag Gln	Arg	atc Ile	aag Lys	gtc Val	tgt Cys	gag Glu 15	aag Lys	cga Arg	ccc Pro	agc Ser	ata Ile 20	gat Asp	147
Met				10										20		
Met cta	tgc Cys	Ile	cac His 25	10 cac His	tgt Cys	tca Ser	tgt Cys	ttc Phe 30	caa	aag Lys	tgt Cys	gaa Glu	aca Thr	aat Asn	aag Lys	195

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Ile Cys Cys Ser Ala Phe Cys Gly Asn Ile Cys Met Ser Ile Leu
40 45 50

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aag ctg ttt gat gcc ccc ttg tcc atc agc aag aga gag cag ctg gaa Lys Leu Phe Asp Ala Pro Leu Ser Ile Ser Lys Arg Glu Gln Leu Glu	160
cag cag gtc cca gag aac tac ttc tat gtg cca gac ctg ggc cag gtg Gln Gln Val Pro Glu Asn Tyr Phe Tyr Val Pro Asp Leu Gly Gln Val 25 30 35 40	208
Cct gag att gat gtt cca tcc tac ctg cct gac ctg ccc ggc att gcc Pro Glu Ile Asp Val Pro Ser Tyr Leu Pro Asp Leu Pro Gly Ile Ala 45 50	256
aac gac ctc atg tac att gcc gac ctg ggc ccc ggc att gcc ccc tct Asn Asp Leu Met Tyr Ile Ala Asp Leu Gly Pro Gly Ile Ala Pro Ser 60 65 70	304
gcc cct ggc acc att cca gaa ctg ccc acc ttc cac act gag gta gcc Ala Pro Gly Thr Ile Pro Glu Leu Pro Thr Phe His Thr Glu Val Ala 75 80 85	352
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ttg atc ttc ggt ctc gga gca gtt tgg ggg ctt ggt gtg gac cct tcc Leu Ile Phe Gly Leu Gly Ala Val Trp Gly Leu Gly Val Asp Pro Ser -10 -5 1 5	160
cta cag att gac gtc tta aca gag tta gaa ctt ggg gag tcc acg acc Leu Gln Ile Asp Val Leu Thr Glu Leu Glu Leu Gly Glu Ser Thr Thr	208
gga gtg cgt cag gtc ccg ggg ctg cat aat ggg acg aaa gcc ttt ctc Gly Val Arg Gln Val Pro Gly Leu His Asn Gly Thr Lys Ala Phe Leu 25 30 35	256
ttt caa gat act ccc aga agc ata aaa gca tcc act gct aca gct gaa Phe Gln Asp Thr Pro Arg Ser Ile Lys Ala Ser Thr Ala Thr Ala Glu 40 45 50	304
cag ttt ttt cag aag ctg aga aat aaa cat gaa ttt act att ttg gtg Gln Phe Phe Gln Lys Leu Arg Asn Lys His Glu Phe Thr Ile Leu Val	352
acc cta aaa cag acc cac tta aat tca gga gtt att ctc tca att cac Thr Leu Lys Gln Thr His Leu Asn Ser Gly Val Ile Leu Ser Ile His	400
75 80 85 cac ttg gat cac agg taaatgtggt tgctggagtt tcctgtgttt tcattatatg His Leu Asp His Arg	455
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ttt tgt ctt aga tgt acg tac ttt cct gtt cat tgt ggt atg tgt aat Phe Cys Leu Arg Cys Thr Tyr Phe Pro Val His Cys Gly Met Cys Asn -35 -30 -25	220
ttg cgt tac ttt gaa ttt tcc acg ttt tta ctt tct ttg tct ctc atc Leu Arg Tyr Phe Glu Phe Ser Thr Phe Leu Leu Ser Leu Ser Leu Ile -20 -15 -10	268

act ' Thr ' -5																316
cta Leu					-	_										361
tgaa	gctt	tc c		ttat	g tg	caga	ttat		caga	ıggg	tata	taga		cago	caget	421
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Leu																
	-5					1				5					10	
att Ile								ttt								148
116	FIO	GIY	GIII	15	мта	GIII	neu	FIIC	20	ıyı	GIII	Mec	361	25	GIII	
caa	cta	cag	cag	cag	cct	tcg	gct	aac		aaa	gca	gga	aaa	atc	cac	196
Gln	Leu	Gln	Gln	Gln	Pro	Ser	Ala	Asn	Lys	Lys	Ala	Gly	Lys	Ile	His	
			30					35					40			244
Asn								aat Asn								244
••••		45	- 110		11011	0111	50			****	0111	55			2,5	
								cgt								292
Pro		Gln	Gln	Ile	Leu		Gly	Arg	Gln	Ser	_	Ser	Leu	Thr	Ser	
CCS	60	cta	act	+00	tas	65		aacta	22501		70	ara a		~c++/	stet	347
Pro			_	_	Lyac	accı	Laa	aucce	aacci		aayaa	19905	, aa	geee		347
75				- 2 -												
															cgggag	407
															aatgaa	467
		-	_	_	_				_					_	gacagg ttaaga	527 587
						-	_				_		_		ttctct	647
_		_	_		_	_		_					_	-	atgttc	707
cctt	aago	caa a	aatto	aati	tt go	cttt	gaac	t tti	tagt	tatg	caca	agact	tga 1	taat	aaacct	767
ctas	2001	-00 /	~~~~	.~~~	~ + ·							2020			taaass	027

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ccaacaccag gaagagtct agctgccaaa caagtacgg cac att tta caa ctg His Ile Leu Gln Leu -40 gta cat tgt cct gac Val His Cys Pro Asp	t agttctgaaa ctt act aca Leu Thr Thr -35 act gga aaa	atccagaatg gtg gat gat Val Asp Asp gac att tgg	gga att caa Gly Ile Glr -30 aat tta ctt	Met 164 164 164 164 164 164 164 164 164 164
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gcg Ala	Ile	Gly	gct Ala 1	Asp	Ser	Ala	Arg 5	Phe	Glu	Glu	Leu	Leu 10	Leu	Gln	Ala	
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~~~	242	200	acc			+ ממים	aaa	ggee			tata	tcat	c ta		ctta	955
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aaa	a gc	ı aga	1 CCI	. gal	L CCC	ኔ UCAN ን ጥላታ፣	- 95°	, aay	, aai	. aag	, ccc	Ser	r Thi	CV	s Arg	
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1.

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gcc Ala tcg Ser gcc Ala agt Ser 40 aag Lys aag Lys gta Val	gcg Ala caa Gln cta Leu 25 gac Asp gca Ala aaa Lys gaa Glu gct	ggc Gly aac Asn 10 gag Glu tct Ser tca Ser tgt Cys agg	gaggatg to the ctt Leu aag Lys gca Ala gag Glu ttt Phe caa Gln 75 aag Lys gat	gggggggggggggggggggggggggggggggggggggg	gaa Glu	gag of slu I gta Val aag Lys ctt Leu 30 gag Glu gcc Ala ggc Cys aga	atc Ile cgc Arg 15 tcc Ser gag Glu tct Ser cca Pro cac His 95 aag	tca Ser cgc Arg cag Gln gaa Glu gct Ala cct Pro aaa Lys	cga Arg Cag Gln cat His agg Arg gaa Glu 65 tgc Cys cag Gln	gcc cdla (classification) ctc Leu ccc Pro daag Lys 50 gta Val agt Ser gct Ala	ccg Pro ttg Leu ccc Pro 35 aag Lys Gly gac Asp ctt Leu	gcg cclar Pro gcc Ala 20 agc Ser aaa Lys tct Ser gtt Val 100 aaa	gcg (Ala I gcg Ala 5 aca Thr cta Leu tgc Cys aaa Lys gag Glu 85 ggc Gly cat	gcc Ala tta Leu tgt Cys ccc Pro ggg Gly 70 gaa Glu agt Ser	ta Val 10 tcc Ser cgg Arg ata Ile aaa Lys 55 aag Lys gaa Glu gac Asp cct	109 157 205 253 301 349 397 445

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	Asn	Ser	Ala	Gln		Leu	Asp	Asn	Val		Gln	Thr	Gly	Pro	Lys . 135	-
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Ala	rgg Tro	Lvs	Glv	Ser	Thr	Thr	Asn	Asp	Pro	Pro	Lys	Gln	Ser	Pro	Gly	
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Ser	Thr	Ser		Lys	Pro	Pro	His		Leu	Ser	Arg	Lys		Trp	Arg	
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aac Asn	Cgg.	Caa	Lve	Aar Aen	Lvs	Ara	Ara	Cvs	Lvs	Asn	Lvs	Phe	Gln	Pro	Pro	
Veri	AT 9	170	цу	no	<i>D</i> ₁ <i>D</i>	**** 5	175	-1-	-1-		-1-	180				
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Gln		Pro	Asp	Gln	Ala		Ala	Glu	Ala	Pro		Glu	Lys	Thr	Glu	
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gtg	tct	CCT	gtt	CCC	agg	aca	gac	Ser	Hie	999 61v	Δla	Ara	Ala	G) A	Ala	,01
200	Ser	PIO	Val	PIO	205	1111	АБР	361	штэ	210	AIG	nr 9	71.14		215	
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Leu	Arg	Ala	Arg	Met	Ala	Gln	Arg	Leu	Asp	Gly	Āla	Arg	Phe	Arg	Tyr	
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ctc	aat	gaa	cag	ttg	tac	tca	999	ccc	agc	agt	gct	gca	cag	cgt	ctc	877
Leu	Asn	Glu		Leu	Tyr	Ser	Gly	Pro	Ser	Ser	Ala	Ala		Arg	Leu	
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Dhe	Cag	Glu	yac Asn	Dro	Glu	Ala	Phe	Leu	Len	Tvr	His	Ara	Glv	Phe	Gln	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,
FIIC	GIM	250	vob	110	OTG	mu	255			-,-		260	1			
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Ser	Gln	Val	Lys	Lys	Trp	Pro	Leu	Gln	Pro	Val	Asp	Arg	Ile	Ala	Arg	
	265					270					275					1001
gat	ctt	cgc	cag	cgg	cct	gca	tcc	cta	gtg	gtg	gct	gac	ttc	ggc	tgt	1021
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Glv	Asp	Cvs	Arq	Leu	Ala	Ser	Ser	Ile	Arg	Asn	Pro	Val	His	Cys	Phe	
				300					305					310		
gac	ttg	gct	tct	ctg	gac	cct	agg	gtc	act	gtg	tgt	gac	atg	gcc	cag	1117
Asp	Leu	Ala		Leu	Asp	Pro	Arg	Val	Thr	Val	Суѕ	Asp			Gin	
			315				~+~	320	~+ ~	aat	ata	+++	325		tra	1165
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Val	FIO	330		rop	GIU	501	335					340				
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Leu	Met	Gly	Thr	Asn	Ile	Arg	Asp	Phe	Leu	Glu	Glu	Ala	Asn	Arg	Val	
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360	гàг	Pro	GIY	GIY	ьец 365		ьys	Val	АТА	370		261	361	Arg	Phe 375	
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Glu	Asp	Val	Arq	Thr	Phe	Leu	Arg	Ala	Val	Thr	Lys	Leu	Gly	Phe	Lys	
	_			380					3 8 5					390		
att	gtc	tcc	aag	gac	ctg	acc	aac	agc	cat	ttc	ttc	ttg	ttt	gat	ttc	1357
Ile	Val	Ser	_		Leu	Thr	Asn			Phe	Phe	Leu			Phe	
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Gla	Lve	Thr	999	Dro	Dro	Len	y y La	ദിച	Pro	aay Lvs	Δla	Gln	Leu	Ser	ggc	1405
2111	Lys	410		-10			415			2,3		420			J	
ctg	cag			сса	tgt	cto			cgc	agg	tga			atct	tccttg	1458
								Lys								
	425				-	430										
aga	9999	agg	caga	tctc	aa a	ctcc	aggo	t ca	gaac	tgtg	aag	actg	ttt	ccgg	cctggc	1518
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1678

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<221> sig_peptide

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<223> Von Heijne matrix

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<223> Von Heijne matrix score 4.1

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							Met	АІА	АТА	ser	-50	Ala	Ala	vaı	vai		
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Ser	Ser	Pro	Ser	Leu	Lys	Thr	Asp	Thr	Ser	Pro	Val	Leu	Glu.	Thr	Ala		
-45					-40					-35					-30		
qqa	acq	qtc	gca	gca	atg	gct	gcg	acc	ccg	tca	gca	agg	gct	gca	gcc	14	8
Glv	Thr	Val	Ăla	Āla	Met	Āla	Ala	Thr	Pro	Ser	Ala	Arg	Ala	Ala	Ala		
•				-25					-20					-15			
aca	ata	qtt	gcg	qcc	qcq	gcc	agg	acc	gga	tcc	gaa	gcc	agg	gtc	tcc	19	6
Ala	Val	Val	Ala	Ala	Ala	Ala	Arg	Thr	Gly	Ser	Glu	Ala	Arg	Val	Ser		
			-10				_	-5	-				1				
aad	acc	act	ttg	act	acc	aaq	ctq	ctq	tcc	ttq	agc	ggc	gtg	ttc	gcc	24	4
Lvs	Ala	Ala	Leu	Ala	Thr	Lvs	Leu	Leu	Ser	Leu	Ser	Gly	Val	Phe	Ala		
-7-	5					10					15	•					
ata	cac	aaq	ccc	aaa	ggg	ccc	act	tca	gcc	gag	ctg	ctg	aat	cgg	ttg	29	92
Val	His	Lys	Pro	Lys	Gly	Pro	Thr	Ser	Āla	Glu	Leu	Leu	Asn	Arg	Leu		
20		•		•	25					30					35		
aaq	qaq	aaq	ctg	ctg	gca	gaa	gct	gga	atg	cct	tct	cca	gaa	tgg	acc	34	0
Lvs	Glu	Lys	Leu	Leu	Āla	Glu	Āla	Gly	Met	Pro	Ser	Pro	Glu	Trp	Thr		
-		-		40					45					50			
aag	agg	aaa	aag	cag	act	ttg	aaa	att	999	cat	gga	ggg	act	cta	gac	38	8
Lys	Arg	Lys	Lys	Gln	Thr	Leu	Lys	Ile	Gly	His	Gly	Gly	Thr	Leu	Asp		
•	_	•	55					60					65				
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Ser	Ala	Ala	Arg	Gly	Val	Leu	Val	Val	Gly	Ile	Gly	Ser	Gly	Thr	Lys		
		70	_	_			75					80					
atg	ttg	acc	agt	atg	ttg	tca	ggg	tcc	aag	agg	tat	act	gcc	att	gga	4 8	34
			Ser														
	85					90					95						
gaa	ctg	999	aaa	gct	act	gat	aca	cta	gat	tct	acg	ggg	aag	gta	aca	53	32
Glu	Leu	Gly	Lys	Ala	Thr	Asp	Thr	Leu	Asp	Ser	Thr	Gly	Lys	Val	Thr		
100		_	-		105	-				110					115		
gaa	gaa	aaa	cct	tac	ggt	atg	aac	ctc	atc	taa	gtag					56	59
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141

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Leu	Leu	Glu -75	Glu	Leu	Pro	Leu	Pro -70	Asp	Gln	Gln	Pro	-65	Ile	GIu	Pro	
cca	cct	tcc	tcc	atc	atg	tac	cag	gct	aac	ttt	gac	aca	aac	ttt	gag	144
	-60					-55					-50	Thr				102
gac	agg	aat	gca	ttt	gtc	acg	ggc	att	gca	agg	tac	att	gag	Cag	gct Ala	192
	Arg	Asn	Ala	Phe	-40	Thr	GIY	116	Ala	-35	ıyı	Ile	Giu	G111	-30	
-45	atc	cac	téc	agc		aat	qaq	atq	ctg		gaa	gga	cat	gag	tat	240
.Thr	Val	His	Ser	Ser	Met	Asn	Glu	Met	Leu -20	Glu	Glu	GIY	HIS	-15	TYF	
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Ala	Val	Met	Leu -10	Tyr	Thr	Trp	Arg	Ser	Cys	Ser	Arg	Ala	1 11e	Pro	GIn	226
gtg	aaa	tgc	aac	gag	cag	ccc	aac	cga	gta	gag	atc	tat	gag	aag	aca	336
	5					10					15	Tyr				204
gta	gag	gtg	ctg	gag	ccg	gag	gtc	acc	aag	ctc	atg	aag	Dhe	atg Met	Tvr	384
Val 20	Glu	Val	Leu	Glu	25	GIU	val	1111	ьуѕ	30	Mec	Lys	rnc	1,00	35	
20 ttt	cad	cac	aag	acc		gag	cgg	ttc	tgc		gag	gtg	aag	cgg	ctg	432
Phe	Gln	Arg	Lys	Ala 40	Ile	Glu	Arg	Phe	Cys 45	Ser	Glu	Val	Lys	Arg 50	ьeu	
tgc	cat	gcc	gag	cgc	agg	aag	gac	ttt	gtc	tct	gag	gcc	tac	ctc	ctg	480
Cys	His	Ala	Glu 55	Arg	Arg	Lys	Asp	Phe 60	Val	Ser	Glu	Ala	Tyr 65	Leu	Leu	. =10
acc	ctt	ggc	aag	ttc	atc	aac	atg	ttt	gct	gtc	ctg	gat	gag	CEA	Lvs	528
		70					75					Asp 80				576
aac	atg	aag	tgc	agc	gtc	aag	aat	gac	Cac Hie	Ser	Δla	tac Tyr	Lvs	Ara	Ala	
ASI	мет 85	гув	Cys	Ser	vaı	90 90	ASII	rop	1110	DCI	95	-1-	_1-	3		
qca	cad	ttc	ctg	cgg	aag	atg	gca	gat	ccc	cag	tct	atc	cag	gag	tcg	624
Ala	Gln	Phe	Leu	Arg	Lys	Met	Ala	Asp	Pro	Gln	Ser	Ile	Gln	Glu	Ser	
100					105					110		+.	200	cac	115 tat	672
cag	aac	ctt	tco	atg	ttc	ctg	gcc	aac Agn	Cac His	aac Asn	Arc	Tle	Thr	Gln	tgt Cys	0,2
GID	ASI	г	Sei	120		. Deu	, AIG	, Apri	125	, ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	5	,		130)	
ctc	cac	cag	caa	ctt	αaa	gtg	atc	cca	ggc	tat	gag	gag	ctg	ctg	gct	720
:Leu	His	Gln	Gln 135	Lev	Glu	Val	Ile	Pro 140	Gly	тут	Glu	Glu	145	Leu	Ala	260
gac	att	gto	aac	ato	: tgt	gtg	gat	tac	tac	gag	aac	aag	ato	tac	ctg	768
Asp	Ile			ılle	Cys	· Val	. Asp 155		туі	GIU	AST	1 Lys 160	met	. гуг	Leu	
a ##		150	, usc ,		cat	ato			: aac	ata	aaa	cto		:		810
Thr	Pro	Ser	Gli	, aac 1 Lys	His	Met	. Lev	Let	ı Lys	Va]	Lys	Lev	Pro	•		
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                        -15
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Gly Leu Val Arg Ser Ser Pro Ser Leu Asp Gln Met Phe Asp Ala Glu
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Ile Phe Asn Ala Leu Thr Cys Ala Leu Gly Leu Leu Tyr Phe Ile Arg
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Arg Gly Lys Gln Cys Leu Asp Phe Thr Val Thr Val His Phe Phe His
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Trp Trp Leu Val Gln Ala Val Cys Ile Ala Leu Met Ala Val Ile Gly
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gag tac ctg tgc atg cgg acg gag ctc aag gag ata ccc ctc aac tca
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Glu Tyr Leu Cys Met Arg Thr Glu Leu Lys Glu Ile Pro Leu Asn Ser
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Ala Pro Lys Ser Asn Val
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                                                                       104
Val Gln Pro Lys Ile Lys His Arg Pro Phe Cys Phe Ser Val Lys Gly
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                     -30
-35
                                                                       152
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His Val Lys Met Leu Arg Leu Val Phe Ala Leu Val Thr Ala Val Cys
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                                                                       200
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 Cys Leu Ala Asp Gly Ala Leu Ile Tyr Arg Lys Leu Leu Phe Asn Pro
 aac ggt cct tac cag aaa aag cct gtg cat gaa aaa aaa gaa gtt ttg
                                                                       248
Asn Gly Pro Tyr Gln Lys Lys Pro Val His Glu Lys Lys Glu Val Leu
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 score 3.5

seg SILAQVLDQSARA/RL

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agg aga cag agg ctg gcc gag ctg cag gcc aaa cac ggg gat cct ggt Arg Arg Gln Arg Leu Ala Glu Leu Gln Ala Lys His Gly Asp Pro Gly -45 -35 -30	99
gat gcg gcc caa cag gaa gca aag cac agg gaa gca gaa atg aga aac Asp Ala Ala Gln Gln Glu Ala Lys His Arg Glu Ala Glu Met Arg Asn -25 -20 -15	147
agt atc tta gcc caa gtt ctg gat cag tcg gcc cgg gcc agg tta agt Ser Ile Leu Ala Gln Val Leu Asp Gln Ser Ala Arg Ala Arg Leu Ser -10 -5	195
aac tta gca ctt gta aag cct gaa aaa act aaa gca gta gag aat tac Asn Leu Ala Leu Val Lys Pro Glu Lys Thr Lys Ala Val Glu Asn Tyr 5 10 15	243
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•	•															
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Ala	Leu	ьeu	Arg	ьеи	ьеи	PIO	GIU	50	nr 9	voħ	niu	014	55		5	
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Thr	Arq	Asp	Pro	Glu	Lys	Leu	Āla	Ser	Cys	Asp	Ile	Val	Val	Asp	Val	
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tct	75 ttc	aca	gag	acc	ata		tcc	ctq	tcc	cct		agg	ccg	tgg	cag	387
Ser	Phe	Thr	Glu	Thr	Met	Ser	Ser	Leu	Ser	Pro	Gly	Arg	Pro	Trp	Gln	
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Thr	Lys	Leu	Ser	Ser	Ala	Gly	Leu	Ile	Tyr	Leu	His	Pne	GIY	120	гув	
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ьeu	nea	Ala	125	пец	Бец	Gry	****	130	014		F		135		-	
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Asn	His	Pro	Asp	Gln		Thr	Glu	Ala			Lys	Arg	ATA	200	Asp	
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Trp	Leu			Arg	Ala	Leu			Glu	Ala	Let	. Ala	GIR	Arg	Pne	
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cag	gtg) gad	o Dro	Ser	. gga . clv	gay Glu	Tle	Val	Glu	Lev	ı Ala	Lys	Gly	Ala	Cys	
GII	235		, ,,,	, 501		240					245	5	_			
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Pro	Tr	Ly	s Glu	ı His	Lev	Tyr	His	Lev	Glu	ı Sei	. GTA	Lev	ser	Pro	Pro	
250)				255					260				t tac	265	915
gtg	ge	ato	c tto	ttt Dbo	gtt	ato	יינים	act Thr	. gac	: Cag) GC	- 99°	Glı	res	cga Arg	
va.	LAI	1 11	e PIIt	270		. 116	. 171		275		• ••••	,		280)	
ata	a cad	a ta	t ata	ccc	aac	gag	ccc	cac	tca	a tto	caa	a ago	cgs	g cts	ccc	963
Ile	Gli	a Cy	s Va	Pro	Lys	Glu	Pro	His	Ser	r Phe	e Gli	n Sei	c Arg	д гел	Pro	
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cts	g cca	a ga	g cca	a tgg	cgg	ggt	ctt	cgg	ggad	gag	g gc	C CES	g gad	c cas	g gtc	1011
Lei	ı Pro	30 30		o Tri	Arç	4 GT)	, тел 303		, AS	ונטיי	n WT	310	, as)	, ,,,,	n Val	
agi	r aa	oc at	ט כ ככו	t aad	t ta	ato			cat	t qc	a ag			c at	ggc	1059
Se	r Gl	y Il	e Pr	o Gly	Cy	; Ile	Phe	e Va.	l Hi	s Ãl	a Se	r Gl	y Ph	e Il	e Gly	
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99	t ca	c cg	c ac	c cga	a gag	g ggt	gc:	c tt	gag	c at	g gc	c cg	t gc	c ac	t ttg	1107
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Al	a Gl	n Ar	or Se	r Ty:	r Lei	u Pro	o G1:	n Il	e Se	r	J					
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Leu Leu Val Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala
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gea get cet ate cat gat get gae gee caa gag age tee ttg ggt ete
Ala Ala Pro Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu
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Thr Gly Leu Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys
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Gly Asn Leu Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp
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 Phe Arg Gly Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His
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 Gln Leu Gly Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Val
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 Asp Ser Phe His Thr Glu Leu His Pro Arg Val Ala Phe Trp Ile Ile
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 Lys Leu Pro Arg Arg Ser His Gln Asp Ala Leu Glu Gly Gly His
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 Arg Lys Gly Thr His Lys Asp Val Leu Glu Glu Gly Thr Glu Ser Ser
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Cys	Cys	Lys	Gly	Gly	Pro	Asp -50	Glu	Asp	Ala	Val	Glu -45	Arg	Gln	Arg	Arg	
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-40		Leu			-35					-30					-25	
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25					30					35					40	391
cgc Ara	atg Met	tgg Trp	cag Gln	tgc Cvs	cgg	caa Gln	Cys	tac Tyr	cgc Arg	Gln	Met	Cys	Asn	Ala	Leu	371
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		Ile					aay	,	צבבב	,-409	ים יים		,,,,,	<i>-</i>		
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Asn Asp Ser Gln Leu Ser Ala Ser Phe Leu Gln Pro Ser Leu Gln Ala
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                                 -25
            -30
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Asn Cys Pro Ala Leu Asp Pro Ala Val Ser Leu Ser Ala Pro Ala Phe
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Asp Phe Leu Arg Ser Leu Ser Asp Gly Asp Ser Gly Thr Ser Glu His
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                                                                       291
 Ile Ser Ala Val Val Thr Ser Pro Arg Ile Ser Cys His Gly Ala Ala
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 age ace tgagetetet getgattget \gtteeteeca gtetgtggaa getttgeeca
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 Ser Thr
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cad	aag	tg	c cas	gto	gto	tto	ttt	cto	cto	gct	gct	gco	tto	: ננ	tet	825

(1997) (1994)

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Gln Gly His Gln Leu Phe His Ile Phe Leu Val Leu Cys Thr Leu Ala	
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Met Asp Asn Arg Phe Ala Thr Ala -20 -15  ttt gta att gct tgt gtg ctt agc ctc att tcc acc atc tac atg gca Phe Val Ile Ala Cys Val Leu Ser Leu Ile Ser Thr Ile Tyr Met Ala -10 -5 1 gct tcc att ggc aca gac ttc tgg tat gag tat cga agt cca gtt caa Ala Ser Ile Gly Thr Asp Phe Trp Tyr Glu Tyr Arg Ser Pro Val Gln 5 10 15 20 gaa aat tcc agt gat ttg aat aaa agc atc tgg gat gaa ttc att agt Glu Asn Ser Ser Asp Leu Asn Lys Ser Ile Trp Asp Glu Phe Ile Ser 25 30 35 gat gag gca gat gaa aag act tat aat gat gca ctt ttt cga tac aat	150
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Lys	Gly		Ile	Gln	Gly	Gln		Leu	Ser	Ala	Tyr		Ala	Pro	Ser	
		105			~~~		110				++-	115	~+~	+-+	att	482
					ggc Gly											402
PIU	120	AIG	птэ	SCI	GIY	125	птэ	Arg	TAT	GIII	130	FIIC	VAI	171	HCG	
cag		gga	aag	gtc	atc		ctc	ctt	ccc	aag		aac	aaa	act	cga	530
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					gac											578
Gly	Ser	Trp	Lys		Asp	Arg	Phe	Leu		Arg	Phe	His	Leu		Glu	
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	_	_			cag		_		_			_	_			626
PIO	GIU	Ala	170	Inr	Gln	Pne	mec	175	GII	ASI	Tyr	GII	180	Ser	PIO	1
acc	ctc	cad		ccc	aga	maa.	agg	-	acc	aaa	ccc	aad		222	aac	674
					Arg											
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cag	gcg	gag	ata	gct	gcc	tgc	taga	atago	ecg g	gctti	tgcca	at c	eggge	catg	t	725
_					Ala	_	_	_	- '		-			_		
	200					205										
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                                                                       109
               Met Ile Ala Arg Arg Asn Pro Val Pro Leu Arg Phe
                   -40
                                        -35
ctg ccg gat gag gcc cgg agc ctg ccc ccg ccc aag ctg acc gac ccg
                                                                       157
Leu Pro Asp Glu Ala Arg Ser Leu Pro Pro Pro Lys Leu Thr Asp Pro
                -25
                                     -20
egg etc etc tac atc gge tte ttg gge tac tge tec gge etg att gat
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Arg Leu Leu Tyr Ile Gly Phe Leu Gly Tyr Cys Ser Gly Leu Ile Asp
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                                 -5
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Asn Leu Ile Arg Arg Arg Pro Ile Ala Thr Ala Gly Leu His Arg Gln
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ctt cta tat att acg gcc ttt ttt ttg ctg gat att atc ttg
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Leu Leu Tyr Ile Thr Ala Phe Phe Leu Leu Asp Ile Ile Leu
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30 35 40	
gtt aaa aag att gca atg cga gaa gtc aag tta cta aag caa ctt agg	616
Val Lys Lys Ile Ala Met Arg Glu Val Lys Leu Leu Lys Gln Leu Arg 45 50 55	
cat gaa aac ttg gtg aat ctc ttg gaa gtg tgt aaa aaa aaa a	659
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get acc agc ctg get ggc cct gtc ctg tcc acc ctc att gcc cca act Ala Thr Ser Leu Ala Gly Pro Val Leu Ser Thr Leu Ile Ala Pro Thr -10 -5 ccc atg ttg ttt tgt gaa gat aaa agc tgg gat ctt ttt ctt ttt Pro Met Leu Phe Cys Glu Asp Lys Ser Trp Asp Leu Phe Leu Phe Phe 10 15 aag tct cac aag aca tgg ggc atc tcc aca aat tta agt tcc tgt cca Lys Ser His Lys Thr Trp Gly Ile Ser Thr Asn Leu Ser Ser Cys Pro 25 30 35 ttt gga aat ttg ttt cta tgt gta cag ttt gtc aga gaa aaa caa agt Phe Gly Asn Leu Phe Leu Cys Val Gln Phe Val Arg Glu Lys Gln Ser 40 45 ttt tgt atg aat aca gaa tgt gat tta cgc aag aat tgacaaaaaa Phe Cys Met Asn Thr Glu Cys Asp Leu Arg Lys Asn 55 60 60 65 aaaaaaaaa	103 151 199 247
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                        -50
                                             -45
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                                                                      216
Ser Phe Gly Ala Glu Pro Ser Ala Pro Gly Gly Gly Gly Ser Pro Gly
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                                         -30
gee tge eee gee etg ggg aeg aag age tge age tee tee tgt geg gat
                                                                      264
Ala Cys Pro Ala Leu Gly Thr Lys Ser Cys Ser Ser Ser Cys Ala Asp
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                                     -15
tee tit git tet tee tet tee tet cag eet gia tet eta tit teg acc
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Ser Phe Val Ser Ser Ser Ser Gln Pro Val Ser Leu Phe Ser Thr
tca caa gag gga ttg agc tct ctt tgc tct gat gag cca tct tca gaa
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Ser Gln Glu Gly Leu Ser Ser Leu Cys Ser Asp Glu Pro Ser Ser Glu
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att atg act tct tcc ttt ctt tca tct tct gaa ata cat aac act ggc
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Ile Met Thr Ser Ser Phe Leu Ser Ser Ser Glu Ile His Asn Thr Gly
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Phe Pro Asn Glu Phe Ile Val Glu Thr Lys Ile Cys Gln Glu 185 190 195	675
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gac tgg act ctg tca cca gga gag cac gcc aag gac gaa tat gtg cta Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu 20 25 30	157
tac tat tac tcc aat ctc agt gtg cct att ggg cgc ttc cag aac cgc Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg 35 40 45	205
gta cac ttg atg ggg gac atc tta tgc aat gat ggc tct ctc ctg ctc Val His Leu Met Gly Asp Ile Leu Cys Asn Asp Gly Ser Leu Leu Leu 50 55 60	253
Caa gat gtg caa gag gct gac cag gga acc tat atc tgt gaa atc cgc Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg 65 70 75 80	301
ctc aaa ggg gag agc cag gtg ttc aag aag gcg gtg gta ctg cat gtg Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val 85 90 95	349

1,7. 1,75

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tgg gga gcc gag aag ggt gaa tca cct gag gtc agc agt ttt gag acc Trp Gly Ala Glu Lys Gly Glu Ser Pro Glu Val Ser Ser Phe Glu Thr	517
agg ctg gcc aac atg gcg aaa ccc tgt ctc tac tgaaaataca aaaattagct Arg Leu Ala Asn Met Ala Lys Pro Cys Leu Tyr 15 20 25	570
gggtgtggtg gcgggcgcct gtagtcccag ctacttggga gactgaggca ggagaattgc ttgaacacgg aaggcggaag ttgcagtaag ctgagatcgt gccaccgcac accagcttgg gcaacagagt gagactccct ctcaaaaaaa aaaaa	630 690 725

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tta ggg tct acc ata ata cct cat ttt aac tta atc acc ttt gta aag Leu Gly Ser Thr Ile Ile Pro His Phe Asn Leu Ile Thr Phe Val Lys 20 25 30	216
acc ttt ttc caa ata tagtcactct ctgaggtact gatggttagg atctcaacat Thr Phe Phe Gln Ile 35	271
accttttttg ggaggacaca attgaaccca taacagggtg tttgcaagga agagttaaaa tttgaaagaa aggtggtatt tgcttagata gatagggcac agctttctag gtgacaaaaa aaaaaaaaa	331 391 400
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gaa ccc ccg ctc ttg ctt ggt gtt ctg cat cca aat acg aag ctg cga Glu Pro Pro Leu Leu Gly Val Leu His Pro Asn Thr Lys Leu Arg 20 25 30	265
cag gca gaa agg ctg ttt gaa aat caa ctt gtt gga ccg gag tcc ata Gln Ala Glu Arg Leu Phe Glu Asn Gln Leu Val Gly Pro Glu Ser Ile 35 40 45	313
gca cat att ggg gat gtg atg ttt act ggg aca gca gat ggc cgg gtc Ala His Ile Gly Asp Val Met Phe Thr Gly Thr Ala Asp Gly Arg Val	361

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	Lys	Leu	Glu	Asn	-	Glu	Ile	Glu	Thr		Ala	Arg	Phe	Gly	Ser		٠.
65					70				٠.	75					80		455
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GIY	Pro	Cys	ьуs	Thr 85	Arg	Asp	Asp	GIu	Pro 90	vai	Cys	GIY	Arg	Pro 95	ьeu		
aat	ato	cat	ac=			22t		act		+++	ata	acc	ast	gca	tac		505
Glv	חום	Ara	yca Δla	999	Dro	Acn	999 999	Thr	Len	Dhe	y-1	ycc ala	Acn	Ala	Cvs		303
Gry		,9	100	O ₁	110	ASII	OI,	105	DCu	1110	V 11	mu	110	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	C, D		
aaq	qqa	cta		qaa	qta	aat	ccc		aaa	cat	gaa	ata		ctg	ctq		553
_					-					_	-			Leu			
•	_	115					120	-	•	-		125	-				
ctg	tcc	tcc	gag	aca	ccc	att	gag	999	aag	aac	atg	tcc	ttt	gtg	aat		601
Leu	Ser	Ser	Glu	Thr	Pro	Ile	Glu	Gly	Lys	Asn	Met	Ser	Phe	Val	Asn		
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														gat			649
_	Leu	Thr	Val	Ser		Asp	Gly	Arg	Lys		Tyr	Phe	Thr	Asp			
145					150					155					160		600
_	_				-	_	_		_		_		_	gag			697
ser	Ser	ьys	Trp	165	Arg	Arg	ASP	Tyr	170	Leu	Leu	vaı	Met.	Glu 175	GIY		
aca	nat	gac	aaa		cta	cta	nan	tat		act	ata	200	ann	gaa	ota		745
														Glu			, 13
		TID P	180	1119				185	_		• • • •		190		• • • •		
aaa	qtt	tta		qac	caq	ctq	cqq			aat	qqa	atc		ctg	tct		793
	_		_	_	_	_			-			_		Leu			
-		195		-			200				-	205					
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			-					_					_	agc			937
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                                                                      112
                            Met Phe Ala Pro Ala Val Met Arg Ala
                                     -30
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                                                                      160
Phe Arg Lys Asn Lys Thr Leu Gly Tyr Gly Val Pro Met Leu Leu
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                                 -15
att gtt gga ggt tct ttt ggt ctt cgt gag ttt tct caa atc cga tat
                                                                      208
Ile Val Gly Sly Ser Phe Gly Leu Arg Glu Phe Ser Gln Ile Arg Tyr
        -5
                            1
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Asp Ala Val Lys Ser Lys Met Asp Pro Glu Leu Glu Lys Lys Leu Lys
                    15
                                        20
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Glu Asn Lys Ile Ser Leu Glu Ser Glu Tyr Glu Lys Ile Lys Asp Ser
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Lys Phe Asp Asp Trp Lys Asn Ile Arg Gly Pro Arg Pro Trp Glu Asp
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Pro Asp Leu Leu Gln Gly Arg Asn Pro Glu Ser Leu Lys Thr Lys Thr
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score 9.5

SEE LMCLSLCTAFALS/KP

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His Trp Tyr Ser Pro Pro Glu Arg Thr Gly Ile Ser Leu Ile Leu Thr

55

65

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tca Ser gcg Ala aca Thr	agg Arg gng Xaa atc Ile 1	gtt Val gan Xaa -15 tgg Trp	atg Met -30 ctg Leu tta Leu	tca Ser ctt Leu ttt Phe	gaa Glu gtc Val aaa Lys 5	aag Lys ttc Phe aat Asn	gat Asp aat Asn -10 cat His	gag Glu -25 ttt Phe cga Arg	tat Tyr ttg Leu ttc Phe	cag Gln ctc Leu cgc Arg 10	ttt Phe atc Ile ttc Phe	Caa Gln Ctt Leu -5 ttg Leu att	cat His -20 acc Thr cat His	can Xaa att Ile gaa Glu	rg Gln 55 nna Xaa ttg Leu act Thr 15 tat	105 153 201
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cccctatctc cagacctcat tcgcaatgaa gtagaatgtc tgaaagcaga tttcaaccac agaatcaagg aggttetett caactecetc ttcagtgcct actatgttgc attetececc ctgtgttttg tgaagagtac ccagtactat gac atg cgc tgg tca tgt gag cac Met Arg Trp Ser Cys Glu His -115 -110 ctc gtt atg gtg tgg atc aat gct ttt gtc atg ctc acc acg caa ctg Leu Val Met Val Trp Ile Asn Ala Phe Val Met Leu Thr Thr Gln Leu -105 -100 -95 ttg cca tcc aaa tac tgt gat ttg cta cat aaa tca gct gct cac ctg Leu Pro Ser Lys Tyr Cys Asp Leu Leu His Lys Ser Ala Ala His Leu -90 -85 -80 ggc aag tgg cag aag ttg gaa cat ggg tcc tac agc aat gct cca cag Gly Lys Trp Gln Lys Leu Glu His Gly Ser Tyr Ser Asn Ala Pro Gln -75 -65 cac att tgg tca gaa aat aca ata tgg cct caa ggg gtg ctg gtg cgg His Ile Trp Ser Glu Asn Thr Ile Trp Pro Gln Gly Val Leu Val Arg -60 -55 -50 -45 cac agc aga tgt tta tat aga gcc atg ggg cct tac aac gtg gca gtg His Ser Arg Cys Leu Tyr Arg Ala Met Gly Pro Tyr Asn Val Ala Val -40 -35 -30	120 174 222 270
cccctatctc cagacctcat tcgcaatgaa gtagaatgtc tgaaagcaga tttcaaccac agaatcaagg aggttctctt caactccctc ttcagtgcct actatgttgc atttctcccc ctgtgttttg tgaagagtac ccagtactat gac atg cgc tgg tca tgt gag cac Met Arg Trp Ser Cys Glu His -115 -110 ctc gtt atg gtg tgg atc aat gct ttt gtc atg ctc acc acg caa ctg Leu Val Met Val Trp Ile Asn Ala Phe Val Met Leu Thr Thr Gln Leu -105 -100 -95 ttg cca tcc aaa tac tgt gat ttg cta cat aaa tca gct gct cac ctg Leu Pro Ser Lys Tyr Cys Asp Leu Leu His Lys Ser Ala Ala His Leu -90 -85 -80 ggc aag tgg cag aag ttg gaa cat ggg tcc tac agc aat gct cca cag Gly Lys Trp Gln Lys Leu Glu His Gly Ser Tyr Ser Asn Ala Pro Gln -75 -65 cac att tgg tca gaa aat aca ata tgg cct caa ggg gtg ctg gtg cgg His Ile Trp Ser Glu Asn Thr Ile Trp Pro Gln Gly Val Leu Val Arg -60 -55 -55 -50 -45 cac agc aga tgt tta tat aga gcc atg ggg cct tac aac gtg gca gtg His Ser Arg Cys Leu Tyr Arg Ala Met Gly Pro Tyr Asn Val Ala Val -40 -35 -30 cct tca gat gta tct cat gcc cgc ttt tat ttc tta ttt cat cga cca Pro Ser Asp Val Ser His Ala Arg Phe Tyr Phe Leu Phe His Arg Pro -25 -20 -15	120 174 222 270 318
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•							
5		10		15			20
tcc atg gct	ctc atc		tqc aac	tac tat	gtt tta	ttt aaa	ctt.
Ser Met Ala	Leu Ile	Leu Phe	Cys Asn	Tyr Tyr	Val Leu	Phe Lys	Leu
	25			30		35	
ctc cgg gac	aga ata	gta tta	ggc agg	gca tac	tcc tac	cca ctc	aac
Leu Arg Asp	Arg Ile	Val Leu	Gly Arg	Ala Tyr	Ser Tyr	Pro Leu	Asn
	40		45			50	
agt tat gaa	ctc aag	gca aac	taagctg	cct ctcaa	acaatg ag	gggagaact	
Ser Tyr Glu	Leu Lys	Ala Asn					
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cagataaaaa t							
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-30 Lys Ser Leu	T T	-25	Cor Nla	Ton Cor		T.ou Ala	T.em
•	Leu Leu	-10	Ser Ara	-5	ped bed	Ded Ara	1
-15 Leu Leu Pro	His Ora		Dro Dhe	-	Acn Leu	Hic Ala	_
Leu Leu PIO	nis cys	GIN bys	10	vai lyi	Asp Dea	15	•41
Lys Asn Asp	Dhe Gln	Tle Trn		The Cvs	Gly Arg		Cvs
Dyb Asii Asp	rne Gin	Tre Trp	25	iic cys	30		-7
Leu Asp Leu	Ive Asp	Thr Phe		Ser Lev		Tvr Asn	Phe
35	Dyo Rop	40	0,0 000		45	-,-	
Arg Ile Phe	Glu Ara		Glv Ser	Arg Lys		Ser Phe	Leu
50		55		60			65
Leu Gly Thr	Trp Val	Leu Ser	Ala Leu	Phe Asp	Phe Leu	Leu Ile	Glu
	70			75		80	
Ala Met Gln	Tyr Phe	Phe Gly	Ile Thr	Ala Ala	Ser Asn	Leu Pro	Ser
	85		90			95	
Gly Leu Ile	Phe Cys	Cys Ala	Phe Cys	Ser Glu	Thr Lys	Leu Phe	Leu
100	_		105		110		
Ser Arg Gln	Ala Met	Ala Glu	Asn Phe	Ser Ile			
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Met Ala Asp		Lys Glu	Phe Leu		Asn Phe		Arg
1	5			10	m1 - 1	15	Dh.
Met Tyr Tyr		Asp Trp		Arg Asn	Phe Ala		Pne
	20		25			30	a)
Phe Met Gly	Lys Val	Ala Leu		lie Trp		ren r	GIN
3.5			40		45		
Lys Gln Lys	Lys Arg	ser Asn					

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Met Pro Val Pro Ala Leu Cys Leu Leu Trp Ala Leu Ala Met Val Thr

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Val Pro Leu Val Gly Leu Ile His Leu Gly Trp Tyr Arg Ile Lys Ser
                     1
           ~ 5
Ser Pro Val Phe Gln Ile Pro Lys Asn Asp Asp Ile Pro Glu Gln Asp
                     15
Ser Leu Gly Leu Ser Asn Leu Gln Lys Ser Gln Ile Gln Gly Lys Xaa
                  30
Ala Gly Leu Gln Ser Ser Gly Lys Glu Ala Ala Leu Asn Leu Ser Phe
                                  50
                 45
Ile Ser Lys Glu Glu Met Lys Asn Thr Ser Trp Ile Arg Lys Asn Trp
                              65
Leu Leu Val Ala Gly Ile Ser Phe Ile Gly Asp His Leu Gly Thr Tyr
                  80
Phe Leu Gln Arg Ser Ala Lys Gln Ser Val Lys Phe Gln Ser Gln Ser
 90 , 95
Lys Gln Lys Ser Ile Glu Glu
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<400> 146

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70 60 Lys Met Ile Ala Asn Asp Val His Thr Leu Arg Arg Ser Lys Ala Thr 85 80 Val Gly Arg Pro Leu Ile Ala Trp Arg Tyr Val Pro Ile Asn Val Val 100 95 Glu Thr Leu Arg Thr Arg Gly Ala Pro Thr Arg Ile Val Arg Lys Val 120 115 Ala Arg Asn Leu Gly Lys Ala Thr Ser Gly Val Leu Val Val Leu Asp 130 135 125 Val Val Asn Leu Val Gln Asp Ser Leu Asp Leu His Lys Gly Glu Lys 145 150 Ser Glu Ser Ala Glu Leu Leu Arg Gln Trp Ala Gln Glu Leu Glu Glu 165 155 160 Asn Leu Asn Glu Leu Thr His Ile His Gln Ser Leu Lys Ala Gly 180

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<222> -49..-1

<400> 147 Met Pro Gly Thr Glu Val Leu Glu Gly Ala Thr Asp Gly Leu Ala Ala -40 -45 Ile Asn Leu Leu Lys Trp Ile Lys Thr Leu Gly Gly Ser Val Ile Ser -25 -20 -30 Met Ile Val Leu Leu Ile Cys Val Val Cys Leu Tyr Ile Val Cys Arg -15 -10 Cys Gly Ser His Leu Trp Arg Glu Ser His His 10 - -- 5

<210> 148 <211> 180 <212> PRT <213> Homo sapiens

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75
80
85
Ser Thr Ile Ser Glu Lys Val Ile Phe Phe Glu Leu Ile Pro Asp Asn
90
95
Met Gly Glu Gln Ala Gln Glu Gln Glu Asp Trp Lys Lys Tyr Ile Thr
110
115
120

Gly Thr Asp Ile Leu Asp Met Lys Leu Glu Asp Ile Leu Val Ser Met 125 130 135

Val Phe

<210> 150 <211> 120 <212> PRT <213> Homo sapiens

<220>
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Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr
60
Cys Ile Arg Ser Lys Asn Gly Pro Gly Thr Ala Val His Ala Tyr Asn
75
Pro Ser Thr Phe Arg Gly Gln Val
90
Fig. Asp Cly Ser Lys Asp Gly Gln Val
95
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<210> 152 <211> 199 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -42..-1

<400> 152 Met Asp Gly Gln Lys Lys Asn Trp Lys Asp Lys Val Val Asp Leu Leu -30 -35 Tyr Trp Arg Asp Ile Lys Lys Thr Gly Val Val Phe Gly Ala Ser Leu -15 -20 -25 Phe Leu Leu Ser Leu Thr Val Phe Ser Ile Val Ser Val Thr Ala 1 -5 Tyr Ile Ala Leu Ala Leu Leu Ser Val Thr Ile Ser Phe Arg Ile Tyr 15 Lys Gly Val Ile Gln Ala Ile Gln Lys Ser Asp Glu Gly His Pro Phe 30 Arg Ala Tyr Leu Glu Ser Glu Val Ala Ile Ser Glu Glu Leu Val Gln 45 50 Lys Tyr Ser Asn Ser Ala Leu Gly His Val Asn Cys Thr Ile Lys Glu 65 60 Leu Arg Arg Leu Phe Leu Val Asp Asp Leu Val Asp Ser Leu Lys Phe 80 Ala Val Leu Met Trp Val Phe Thr Tyr Val Gly Ala Leu Phe Asn Gly 95 100 Leu Thr Leu Leu Ile Leu Ala Leu Ile Ser Leu Phe Ser Val Pro Val 115 110 Ile Tyr Glu Arg His Gln Ala Gln Ile Asp His Tyr Leu Val Leu Ala 130 125 Asn Lys Asn Val Lys Asp Ala Met Ala Lys Ile Gln Ala Lys Ile Pro 145 140 Gly Leu Lys Arg Lys Ala Glu 155

WO 99/31236 <211> 43. <212> PRT <213> Homo sapiens <400> 153 Met Pro Phe Arg Met Ser Gly Tyr Ile Pro Phe Gly Thr Pro Ile Val 10 Ser Val Thr Phe Lys Gly Phe Pro Phe Leu Lys Asn Tyr Phe Lys Cys 25 Leu Thr Leu Cys Tyr Cys Ser Arg Val Phe Asp 35 40 <210> 154 <211> 50 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -37..-1 <400> 154 Met Glu Trp Ala Gly Lys Gln Arg Asp Phe Gln Val Arg Ala Ala Pro -35 -30 -25 Gly Trp Asp His Leu Ala Ser Phe Pro Gly Pro Ser Leu Arg Leu Phe -15 Ser Gly Ser Gln Ala Ser Val Cys Ser Leu Cys Ser Gly Phe Gly Ala 1 5 Gln Glu <210> 155 <211> 153 <212> PRT <213> Homo sapiens

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5 10 His Val His Leu Pro Glu Asn Val Arg Ser Gln Ser Pro Gly His Val 30 25 20 Arg Arg Gly Arg Ser Gly Ala Gln Val Leu Pro Thr Gly Pro Asp Glu 40 Lys Gln Val Glu Lys Ser Glu Val Asp Phe Ser Lys Ser His Ser Leu Val Arg Arg Phe Glu Asp Leu Lys Pro Lys Leu Ser Val Cys Lys Thr 75 70 Gly Ser Gln Val Phe Arg Ser Glu Asn Trp Lys Val Trp Ala Glu Ser 90 85 Ser Arg Gly Asp His Asp Asp Cys Leu Asp Leu Cys Ser Val Leu Cys 105 100 Trp Gly Glu Leu Leu Arg Thr Ile Pro Glu Ile Pro Pro Lys Arg Gly 120 125 Glu Leu Lys Thr Glu Leu Leu Gly Leu Lys Glu Arg Lys His Lys Pro 135 Gln Val Ser Gln Gln Glu Glu Leu Lys 150

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<210> 156
<211> 67
<212> PRT
<213> Homo sapiens
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Leu Thr Ile Gly Asp Val Ile Lys Gln Leu Ile Glu Ala His Glu Gln
            20
                                25
Gly Lys Asp Ile Asp Leu Asn Lys Val Arg Thr Lys Thr Ala Ala Lys
                            40
                                                45
Tyr Gly Leu Ser Ala Gln Pro Arq Leu Val Asp Ile Ile Ala Ala Val
    50
                        55
Pro Pro Glu
65
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<211> 87
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<213> Homo sapiens
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Met Asp Glu Leu Ser Glu Glu Asp Lys Leu Thr Val Ser Arg Ala Arg
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Lys Ile Gln Arg Phe Leu Ser Gln Pro Phe Gln Val Ala Glu Val Phe
                                25
Thr Gly His Met Gly Lys Leu Val Pro Leu Lys Glu Thr Ile Lys Gly
                            40
Phe Gln Gln Ile Leu Ala Gly Glu Tyr Asp His Leu Pro Glu Gln Ala
                        55
Phe Tyr Met Val Gly Pro Ile Glu Glu Ala Val Ala Lys Ala Asp Lys
                    70
                                                             80
Leu Ala Glu Glu His Ser Ser
                85
<210> 158
<211> 250
<212> PRT
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                    -80
                                        -75
Leu Leu Ala Lys Ser Ala Lys Gly Ala Ala Leu Ala Thr Leu Ile His
                -65
                                    -60
Gln Val Leu Glu Ala Pro Gly Val Tyr Val Phe Gly Glu Leu Leu Asp
                                -45
Met Pro Asn Val Arg Glu Leu Xaa Ala Arg Asn Leu Pro Pro Leu Thr
        -35
                            -30
                                                -25
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Glu Ala Gln Lys Asn Lys Leu Arg His Leu Ser Val Val Thr Leu Ala

Ala Lys Val Lys Cys Ile Pro Tyr Ala Val Leu Leu Glu Ala Leu Ala

-10

-15

Leu Arg Asn Val Arg Gln Leu Glu Asp Leu Val Ile Glu Ala Val Tyr · 15 20 Ala Asp Val Leu Arg Gly Ser Leu Asp Gln Arg Asn Gln Arg Leu Glu 35 40 Val Asp Tyr Ser Ile Gly Arg Asp Ile Gln Arg Gln Asp Leu Ser Ala 55 50 Ile Ala Arg Thr Leu Gln Glu Trp Cys Val Gly Cys Glu Val Val Leu 70 65 Ser Gly Ile Glu Glu Gln Val Ser Arg Ala Asn Gln His Lys Glu Gln 85 80 Gln Leu Gly Leu Lys Gln Gln Ile Glu Ser Glu Val Ala Asn Leu Lys 105 100 95 Lys Thr Ile Lys Val Thr Thr Ala Ala Ala Ala Ala Ala Thr Ser Gln 120 115 110 Asp Pro Glu Gln His Leu Thr Glu Leu Arg Glu Pro Ala Pro Gly Thr 130 135 Asn Gln Arg Gln Pro Ser Lys Lys Ala Ser Lys Gly Lys Gly Leu Arg 150 145 Gly Ser Ala Lys Ile Trp Ser Lys Ser Asn 160

<210> 159 <211> 24 <212> PRT <213> Homo sapiens

<400> 159

Met Pro Thr Asn Cys Ala Ala Ala Gly Cys Ala Thr Thr Tyr Asn Lys

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His Ile Asn Ile Ser Phe His Arg
20

<210> 160 <211> 228 <212> PRT <213> Homo sapiens

· <400> 160 Met Pro Thr Asn Cys Ala Ala Ala Gly Cys Ala Thr Thr Tyr Asn Lys His Ile Asn Ile Ser Phe His Arg Phe Pro Leu Asp Pro Lys Arg Arg 25 20 Lys Glu Trp Val Arg Leu Val Arg Arg Lys Asn Phe Val Pro Gly Lys 40 45 His Thr Phe Leu Cys Ser Lys His Phe Glu Ala Ser Cys Phe Asp Leu 60 55 Thr Gly Gln Thr Arg Arg Leu Lys Met Asp Ala Val Pro Thr Ile Phe 75 70 Asp Phe Cys Thr His Ile Lys Ser Met Lys Leu Lys Ser Arg Asn Leu 85 Leu Lys Lys Asn Asn Ser Cys Ser Pro Ala Gly Pro Ser Ser Leu Lys 105 100 Ser Asn Ile Ser Ser Gln Gln Val Leu Leu Glu His Ser Tyr Ala Phe 120 125 Arg Asn Pro Met Glu Ala Lys Lys Arg Ile Ile Lys Leu Glu Lys Glu 140 135 Ile Ala Ser Leu Arg Arg Lys Met Lys Thr Cys Leu Gln Lys Glu Arg and the control of the second second of the second second

155 150 Arg Ala Thr Arg Arg Trp Ile Lys Ala Met Cys Leu Val Lys Asn Leu 170 . 175 165 Glu Ala Asn Ser Val Leu Pro Lys Gly Thr Ser Glu His Met Leu Pro 180 185 190 Thr Ala Leu Ser Ser Leu Pro Leu Glu Asp Phe Lys Ile Leu Glu Gln 195 200 . 205 Asp Gln Gln Asp Lys Thr Leu Leu Ser Leu Asn Leu Lys Gln Thr Lys 215 220 Ser Thr Phe Ile 225

<210> 161 <211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -20..-1

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<210> 162 <211> 44 <212> PRT <213> Homo sapiens

65

<400> 162 Met Ser Pro Arg Leu Glu Cys Ser Gly Ala Ile Leu Ala His Cys Asn 10 Pro Arg Leu Pro Gly Ser Ser Tyr Ser Pro Ala Ser Ala Thr Trp Val 25 20 Arg Gly Ser Leu Glu Pro Gly Arg Leu Arg Leu Gln

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<400> 163 Met Gln Asn Val Ile Asn Thr Val Lys Gly Lys Ala Leu Glu Val Ala -55 -50 Glu Tyr Leu Thr Pro Val Leu Lys Glu Ser Lys Phe Arg Glu Thr Gly -30 -35 Val Ile Thr Pro Glu Glu Phe Val Ala Ala Gly Asp His Leu Val His -15 -20 His Cys Pro Thr Trp Gln Trp Ala Thr Gly Glu Glu Leu Lys Val Lys 1 -5 Ala Tyr Leu Pro Thr Gly Lys Gln Phe Leu Val Thr Lys Asn Val Pro 10 15 Cys Tyr Lys Arq Cys Lys Gln Met Glu Tyr Ser Asp Glu Leu Glu Ala 30 Ile Ile Glu Glu Asp Asp Gly Asp Gly Gly Trp Val Asp Thr Tyr His 45 Asn Thr Gly Ile Thr Gly Ile Thr Glu Ala Val Lys Glu Ile Thr Leu 65 Glu Asn Lys Asp Asn Ile Arg Leu Gln Asp Cys Ser Ala Leu Cys Glu 80 75 Glu Glu Glu Asp Glu Asp Glu Gly Glu Ala Ala Asp Met Glu Glu Tyr 95 Glu Glu Ser Gly Leu Leu Glu Thr Asp Glu Ala Thr Leu Asp Thr Arg 110 115 Lys Ile Val Glu Ala Cys Lys Ala Lys Thr Asp Ala Gly Gly Glu Asp 130 125 Ala Ile Leu Gln Thr Arg Thr Tyr Asp Leu Tyr Ile Thr Tyr Asp Lys 145 140 Tyr Tyr Gln Thr Pro Arg Leu Trp Leu Phe Gly Tyr Asp Glu Gln Arg 155 160 Gln Pro Leu Thr Val Glu His Met Tyr Glu Asp Ile Ser Gln Asp His 170 175 Val Lys Lys Thr Val Thr Ile Glu Asn His Pro His Leu Pro Pro Pro 190 195 Pro Met Cys Ser Val His Pro Cys Arg His Ala Glu Val Met Lys Lys 205 210 Ile Ile Glu Thr Val Ala Glu Gly Gly Glu Leu Gly Val His Met 220 225 Tyr Leu Leu Ile Phe Leu Lys Phe Val Gln Ala Val Ile Pro Thr Ile 235 Glu Tyr Asp Tyr Thr Arg His Phe Thr Met 250

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Ser Thr Gln Pro Val Pro Leu Cys Ser
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                           ~5
Gly Phe Leu Trp Val Trp Asp Ser Ser Glu Arg Met Lys Ser Arg Glu
                               10
Gln Gly Gly Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala
       20
                        25
His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu
                     40
                                         45
Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Val Phe
                   55
                                     60
Arg Arg Glu Leu Ser Glu Tyr Thr Glu Gly Leu Thr Ser Glu Pro Leu
Thr Ala
<210> 166
<211> 92
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -36..-1
<400> 166
Met Leu Val Thr Gln Gly Leu Val Tyr Gln Gly Tyr Leu Ala Ala Asn
                      -30
                                          -25
Ser Arg Phe Gly Ser Leu Pro Lys Val Ala Leu Ala Gly Leu Leu Gly
                  -15
                                    -10
Phe Gly Leu Gly Lys Val Ser Tyr Ile Gly Val Cys Gln Ser Lys Phe
              1
                             5
His Phe Phe Glu Asp Gln Leu Arg Gly Ala Gly Phe Gly Pro Gln His
       15
                          20
                                           25
Asn Arg His Cys Leu Leu Thr Cys Glu Glu Cys Lys Ile Lys His Gly
                       35
                                          40
```

Leu Ser Glu Lys Gly Asp Ser Gln Pro Ser Ala Ser

50

<210> 167 <211> 351 <212> PRT

<213> Homo sapiens

<220>
<221> SIGNAL
<222> -16..-1

<400> 167 Met Val Pro Phe Ile Tyr Leu Gln Ala His Phe Thr Leu Cys Ser Gly -10 Trp Ser Ser Thr Tyr Arg Asp Leu Arg Lys Gly Val Tyr Val Pro Tyr 10 Thr Gln Gly Lys Trp Glu Gly Glu Leu Gly Thr Asp Leu Val Ser Ile 25 20 Pro His Gly Pro Asn Val Thr Val Arg Ala Asn Ile Ala Ala Ile Thr 40 Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser Asn Trp Glu Gly Ile Leu 55 Gly Leu Ala Tyr Ala Glu Ile Ala Arg Pro Asp Asp Ser Pro Glu Pro 70 75 Phe Phe Asp Ser Leu Val Lys Gln Thr His Val Pro Asn Leu Phe Ser 90 85 Leu Gln Leu Cys Gly Ala Gly Phe Pro Leu Asn Gln Ser Glu Val Leu 105 100 Ala Ser Val Gly Gly Ser Met Ile Ile Gly Gly Ile Asp His Ser Leu 115 120 125 Tyr Thr Gly Ser Leu Trp Tyr Thr Pro Ile Arg Arg Glu Trp Tyr Tyr 135 140 Glu Val Ile Ile Val Arg Val Glu Ile Asn Gly Gln Asp Leu Lys Met 150 155 Asp Cys Lys Glu Tyr Asn Tyr Asp Lys Ser Ile Val Asp Ser Gly Thr 165 170 175 Thr Asn Leu Arg Leu Pro Lys Lys Val Phe Glu Ala Ala Val Lys Ser 185 190 180 Ile Lys Ala Ala Ser Ser Thr Glu Lys Phe Pro Asp Gly Phe Trp Leu 200 205 195 Gly Glu Gln Leu Val Cys Trp Gln Ala Gly Thr Thr Pro Trp Asn Ile 215 220 Phe Pro Val Ile Ser Leu Tyr Leu Met Gly Glu Val Thr Asn Gln Ser 230 235 Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr Leu Arg Pro Val Glu Asp 250 245 Val Ala Thr Ser Gln Asp Asp Cys Tyr Lys Phe Ala Ile Ser Gln Ser 265 270 260 Ser Thr Gly Thr Val Met Gly Ala Val Ile Met Glu Gly Phe Tyr Val 275 280 Val Phe Asp Arg Ala Arg Lys Arg Ile Gly Phe Ala Val Ser Ala Cys 295 300 His Val His Asp Glu Phe Arg Thr Ala Ala Val Glu Gly Pro Phe Cys 310 \ 315 His Leu Gly His Gly Arg Leu Trp Leu Gln His Ser Thr Asp Arg

330

<210> 168

<211> 138

<212> PRT

<213> Homo sapiens

325

<220>

<221> SIGNAL

<222> -47..-1

en en la la companya de la companya del companya de la companya del companya de la companya del la companya de la companya de

<400> 168 Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu -40 -35 Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser -30 -25 -20 Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile - 5, -10 Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu . 10 Ala Gly Leu Cys Thr Leu Gly Ser Val Ser Cys Tyr Val Ala Gly Ile 25 Glu Leu Leu His Gln Lys Leu Glu Leu Pro Asp Asn Val Ser Gly Glu Phe Gly Trp Ser Phe Cys Leu Ala Cys Val Ser Ala Pro Leu Gln Phe 55 60 Met Ala Ser Ala Leu Phe Ile Trp Ala Ala His Thr Asn Arg Arg Glu 70 75 Tyr Thr Leu Met Lys Ala Tyr Arg Val Ala

WO 99/31236

<210> 169 <211> 101 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -73..-1 <400> 169 Met Asn Leu Glu Arg Val Ser Asn Glu Glu Lys Leu Asn Leu Cys Arg -70 -65 Lys Tyr Tyr Leu Gly Gly Phe Ala Phe Leu Pro Phe Leu Trp Leu Val -50 -45 -55 Asn Ile Phe Trp Phe Tyr Arg Glu Ala Phe Leu Val Pro Ala Tyr Thr -30 -35 Glu Gln Ser Gln Ile Lys Gly Tyr Val Trp Arg Ser Ala Val Gly Phe -15 -20 Leu Phe Trp Val Ile Val Leu Thr Ser Trp Ile Thr Ile Phe Gln Ile -5 1 Tyr Arg Pro Arg Trp Gly Ala Leu Gly Asp Tyr Leu Ser Phe Thr Ile

15

10 Pro Leu Gly Thr Pro

25

Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -25 -30 -35 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -10 -15 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly 5 Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 55 50 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 70 Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro 85 Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn 100 105 Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu 120 115 Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro 130 135 Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Ser Asp 150 145 Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly 165 Glu Ala Lys Asp Gly Ser Asn Leu Cys Phe Ser Lys 180

<210> 171 <211> 350 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -68..-1

<400> 171 Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu -60 -65 Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -50 -45 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -25 -35 -30 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -10 -5 -15 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly 5 10 1 Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 40 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 50 55 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Glr Glu Tyr Gln Gln Phe 70 Arg Leu Lys Ile Pro Pro Phe Glu Lys Ala Arg Ser Val Leu Glu Ala

85 Leu Gln Gln His Arg Pro Ser Pro Glu Leu Thr Leu Ser Gln Lys Ile 100 105 Arg Thr Lys Leu Gln Asn Pro Asp Leu Leu Glu Leu Cys His Ser Val 115 120 Pro Lys Glu Val Asp Gln Leu Gly Gly Arg Gly Tyr Gly Ser Glu Ser 130 135 Gly Glu Glu Asp Phe Ala Ala Phe Arg Ala Trp Leu Arg Cys Tyr Gly 145 150 Met Pro Gly Met Ser Ser Leu Gln Asp Arg His Gly Arg Thr Ile Trp 160 165 Phe Gln Gly Asp Pro Gly Pro Leu Ala Pro Lys Gly Arg Lys Ser Arg 180 175 185 Lys Lys Lys Ser Lys Ala Thr Gln Leu Ser Pro Glu Asp Arg Val Glu 195 200 Asp Ala Leu Pro Pro Ser Lys Ala Pro Ser Lys Thr Arg Arg Ala Lys 210 215 Arg Asp Leu Pro Lys Arg Thr Ala Thr Gln Arg Pro Glu Gly Thr Ser 225 230 Leu Gln Gln Asp Pro Glu Ala Pro Thr Val Pro Lys Lys Gly Arg Arg 240 245 250 Lys Gly Arg Gln Ala Ala Ser Gly His Cys Arg Pro Arg Lys Val Lys 255 260 265 Ala Asp Ile Pro Ser Leu Glu Pro Glu Gly Thr Ser Ala Ser 275

<210> 172 <211> 390 <212> PRT <213> Homo sapiens

<220>
<221> SIGNAL
<222> -68..-1

<400> 172

Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu -60 -65 Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -30 -25 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -10 -15 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly 1 5 Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 50 55 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 65 70 Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro 85 Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn 100 105 Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu 115

Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro 125 130 135 Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Pro Asp 150 145 Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly 165 160 Gly Arg Gly Tyr Gly Ser Glu Ser Gly Glu Glu Asp Phe Ala Ala Phe 180 Arg Ala Trp Leu Arg Cys Tyr Gly Met Pro Gly Met Ser Ser Leu Gln 195 Asp Arg His Gly Arg Thr Ile Trp Phe Gln Gly Asp Pro Gly Pro Leu 215 220 210 Ala Pro Lys Gly Arg Lys Ser Arg Lys Lys Lys Ser Lys Ala Thr Gln 225 230 235 Leu Ser Pro Glu Asp Arg Val Glu Asp Ala Leu Pro Pro Ser Lys Ala 240 245 250 Pro Ser Arg Thr Arg Arg Ala Lys Arg Asp Leu Pro Lys Arg Thr Ala 260 265 Thr Gln Arg Pro Glu Gly Thr Ser Leu Gln Gln Asp Pro Glu Ala Pro 275 280 Thr Val Pro Lys Lys Gly Arg Arg Lys Gly Arg Gln Ala Ala Ser Gly 290 295 His Cys Arg Pro Arg Lys Val Lys Ala Asp Ile Pro Ser Leu Glu Pro 305 Glu Gly Thr Ser Ala Ser 320

<210> 173 <211> 190 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -82..-1 <400> 173 Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe -75 -70 His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly -55 -60 Val Ser Leu Pro Gly Ile Leu Thr Ala Lys Cys Gly Ala Glu Val Ile -45 -40 Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln -30 -25 -20 Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu Thr -10 Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile 10 Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Asp Phe Glu Asp Ile 25 20 Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln Leu 35 40 Trp Ser Thr Tyr Gln Val Arg Ser Ala Asp Trp Ser Leu Glu Ala Leu 55 Leu Tyr Lys Trp Asp Met Lys Cys Val His Ile Pro Leu Glu Ser Phe 70 75 Asp Ala Asp Lys Glu Asp Ile Ala Glu Ser Thr Leu Pro Gly Arg His 85

Thr Val Glu Met Leu Val Ile Ser Phe Ala Lys Asp Ser Leu

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100

105

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<210> 174
<211> 285
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -232..-1
<400> 174
Met Gly Cys Val Phe Gln Ser Thr Glu Asp Lys Arg Ile Phe Lys Ile
     -230 -225 -220
Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu
                           -205
          -210
Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg
      -195 -190 -185
Val His Leu Met Gly Asp Asn Leu Cys Asn Asp Gly Ser Leu Leu
             -180 -175
Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg
         -165 -160 -155
Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val
           -145
                            -140
      -150
Leu Pro Glu Glu Pro Lys Glu Leu Met Val His Val Gly Gly Leu Ile
                   -130
                                    -125
Gln Met Gly Cys Val Phe Gln Ser Thr Glu Val Lys His Val Thr Lys
-120
                -115
                               -110
Val Glu Trp Ile Phe Ser Gly Arg Arg Ala Lys Glu Glu Ile Val Phe
            -100
                             - 95
Arg Tyr Tyr His Lys Leu Arg Met Ser Ala Glu Tyr Ser Gln Ser Trp
         -85
                         -80
                                  -75
Gly His Phe Gln Asn Arg Val Asn Leu Val Gly Asp Ile Phe Arg Asn
      -70
                       -65
                                       -60
Asp Gly Ser Ile Met Leu Gln Gly Val Arg Glu Ser Asp Gly Gly Asn
  -55
                   -50
                                    -45
Tyr Thr Cys Ser Ile His Leu Gly Asn Leu Val Phe Lys Lys Thr Ile
             -35
                               -30
Val Leu His Val Ser Pro Glu Glu Pro Arg Thr Leu Val Thr Pro Ala
            -20
                             -15
Ala Leu Arg Pro Leu Val Leu Gly Gly Asn Gln Leu Val Ile Ile Val
                        1
Gly Ile Val Cys Ala Thr Ile Leu Leu Leu Pro Val Leu Ile Leu Ile
           15
                                   20
Val Lys Lys Thr Cys Gly Asn Lys Ser Ser Val Asn Ser Thr Val Leu
              30
                    35
Val Lys Asn Thr Lys Lys Thr Asn Pro Lys Lys Lys
             45
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<210> 175

<211> 153

<212> PRT

<213> Homo sapiens

<400> 175

Met Gly Cys Val Phe Gln Ser Thr Val Asp Lys Cys Ile Phe Lys Ile 1 5 10 15 Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu

25 Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg 40 Val His Leu Met Gly Asp Ile Leu Cys Asn Asp Gly Ser Leu Leu 55 Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg 70 75 Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val 90 85 Leu Pro Glu Glu Pro Lys Glu Leu Met Val His Val Gly Gly Leu Ile 110 105 Gln Met Gly Cys Val Phe Gln Ser Thr Glu Val Lys His Val Thr Lys 120 125 Val Glu Trp Ile Phe Ser Gly Arg Arg Ala Lys Val Thr Arg Arg Lys 135 His His Cys Val Arg Glu Gly Ser Gly 150

<210> 176 <211> 49 <212> PRT <213> Homo sapiens

<210> 177 <211> 99 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -24..-1

<213> Homo sapiens

<400> 180

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<210> 178
<211> 95
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 178
Met Ala Ser Pro Ala Val Asn Arg Trp Lys Arg Pro Arg Leu Lys Pro
                            -30
                                                -25
Val Trp Pro Arg Arg Leu Glu Ser Trp Leu Leu Leu Asp Ala Leu Leu
   -20
                        -15
                                            -10
Arg Leu Gly Asp Thr Lys Lys Lys Arg Gln Pro Glu Ala Ala Thr Lys
-5
                    1
                                    5
Ser Cys Val Arg Ser Ser Cys Gly Gly Pro Ser Gly Asp Gly Pro Pro
            15
                                20
Pro Cys Leu Gln Gln Pro Asp Pro Arg Ala Leu Ser Gln Ala Phe Ser
                           35
                                                40
Arg Ser Phe Pro Leu Phe Pro Ser Leu Ala Gly Lys Ser Met Ile
    45
                        50
                                            55
<210> 179
<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 179
Met Met Leu Pro Gln Trp Leu Leu Leu Leu Phe Leu Leu Phe Phe Phe
                                -15
                                                    -10
Leu Phe Leu Leu Thr Arg Gly Ser Leu Ser Pro Thr Lys Tyr Asn Leu
       -5
                            1
Leu Glu Leu Lys Glu Ser Cys Ile Arg Asn Gln Asp Cys Glu Thr Gly
                   15
                                        20
Cys Cys Gln Arg Ala Pro Asp Asn Cys Glu Ser His Cys Ala Glu Lys
                30
                                    35
Gly Ser Glu Gly Ser Leu Cys Gln Thr Gln Val Phe Phe Gly Gln Tyr
            45
                                50
Arg Ala Cys Pro Cys Leu Arg Asn Leu Thr Cys Ile Tyr Ser Lys Asn
                            65
Glu Lys Trp Leu Ser Ile Ala Tyr Gly Arg Cys Gln Lys Ile Gly Arg
                        80
Gln Lys Leu Ala Lys Lys Met Phe Phe
<210> 180
<211> 59
<212> PRT
```

Met Ile Leu Cys Phe Leu Leu Pro His His Arg Leu Gln Glu Ala Arg

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<210> 181 <211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -14..-1 <400> 181 Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp Cys -10 Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Pro Arg Ser Ser Ala 10 Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly Trp 25 Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg Leu 40 45 Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu Gly 60 55

<210> 182 <211> 165 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1

Tyr Arg Ile Cys Asp Leu 70

<400> 182 Met Thr Arg Leu Cys Leu Pro Arg Pro Glu Ala Arg Glu Asp Pro Ile -50 Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser Pro -35 -30 Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu Leu -25 -20 -15 Asp Ser Val Leu Trp Leu Gly Ala Leu Gly Leu Thr Ile Gln Ala Val Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Val Ser Phe Leu 15 Thr Phe Asp Leu Leu His Arg Pro Ala Gly His Thr Leu Pro Gln Arg 30 Lys Leu Leu Thr Arg Gly Gln Ser Gln Gly Ala Gly Glu Gly Pro Gly 45 Gln Gln Glu Ala Leu Leu Gln Met Gly Thr Val Ser Gly Gln Leu 60 65 Ser Leu Gln Asp Ala Leu Leu Leu Leu Leu Met Gly Leu Gly Pro Leu and the second of the second o

```
75
                                   80
                                                       85
 Leu Arg Ala Cys Gly Met Pro Leu Thr Leu Leu Gly Leu Ala Phe Cys
           90
                               95
 Leu His Pro Trp Ala
        105
 <210> 183
 <211> 80
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -35..-1
 <400> 183
 Met Pro Phe Gln Phe Gly Thr Gln Pro Arg Arg Phe Pro Val Glu Gly
           -30
                                      -25
Gly Asp Ser Ser Ile Glu Leu Glu Pro Gly Leu Ser Ser Ser Ala Ala
                                  -10
Cys Asn Gly Lys Glu Met Ser Pro Thr Arg Gln Leu Arg Arg Cys Pro
            1
                                        10
Gly Ser His Cys Leu Thr Ile Thr Asp Val Pro Val Thr Val Tyr Ala
    15
                    20
Thr Thr Arg Lys Pro Pro Ala Gln Ser Ser Lys Glu Met His Pro Lys
                   35
                                     40
<210> 184
<211> 73
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 184
Met Ala Pro Gln Thr Leu Leu Pro Val Leu Val Leu Cys Val Leu Leu
  -20 · -15
                                         -10
Leu Gln Ala Gln Gly Gly Tyr Arg Asp Lys Met Arg Met Gln Arg Ile
-5
                  1
Lys Val Cys Glu Lys Arg Pro Ser Ile Asp Leu Cys Ile His His Cys
                              20
Ser Cys Phe Gln Lys Cys Glu Thr Asn Lys Ile Cys Cys Ser Ala Phe
       30
                         35
                                            40
Cys Gly Asn Ile Cys Met Ser Ile Leu
   45
<210> 185
<211> 98
<212> PRT
<213> Homo sapiens
<400> 185
Met Leu Gly Ala Glu Thr Glu Glu Lys Leu Phe Asp Ala Pro Leu Ser
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 Ile
 Ser
 Lys
 Arg
 Glu
 Gln
 Leu
 Glu
 Gln
 Gln
 Gln
 Val
 Pro
 Glu
 Asn
 Tyr
 Phe

 Tyr
 Val
 Pro
 Asp
 Leu
 Gly
 Gln
 Val
 Pro
 Glu
 Ile
 Asp
 Val
 Pro
 Ser
 Tyr

 Leu
 Pro
 Asp
 Leu
 Pro
 Gly
 Ile
 Ala
 Pro
 Ser
 Ala
 Pro
 Gly
 Thr
 Ile
 Ala
 Asp
 Leu
 Met
 Tyr
 Ile
 Ala
 Asp

 Leu
 Gly
 Pro
 Gly
 Ile
 Ala
 Pro
 Ser
 Ala
 Pro
 Gly
 Thr
 Ile
 Pro
 Glu
 Leu

 Fro
 Thr
 Pro
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 Ala
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 Ile
 Ala
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 I

<210> 186 <211> 112 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

<210> 187

Glu Trp Gly Leu Leu Arg

<400> 186 Met Glu Ser Arg Val Leu Leu Arg Thr Phe Cys Leu Ile Phe Gly Leu -15 -10 Gly Ala Val Trp Gly Leu Gly Val Asp Pro Ser Leu Gln Ile Asp Val 1 Leu Thr Glu Leu Glu Leu Gly Glu Ser Thr Thr Gly Val Arg Gln Val 15 Pro Gly Leu His Asn Gly Thr Lys Ala Phe Leu Phe Gln Asp Thr Pro 35 Arg Ser Ile Lys Ala Ser Thr Ala Thr Ala Glu Gln Phe Phe Gln Lys 50 Leu Arg Asn Lys His Glu Phe Thr Ile Leu Val Thr Leu Lys Gln Thr 65 His Leu Asn Ser Gly Val Ile Leu Ser Ile His His Leu Asp His Arg 85

<211> 70 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -44..-1 <400> 187 Met Cys Cys Tyr Cys Arg Ile Phe Cys Leu Arg Cys Thr Tyr Phe Pro -35 -40 Val His Cys Gly Met Cys Asn Leu Arg Tyr Phe Glu Phe Ser Thr Phe -20 -25 Leu Leu Ser Leu Ser Leu Ile Thr Tyr Cys Phe Trp Asp Pro Pro His -5 Arg Gly Ser His Ser Leu Ser Leu Glu His Thr Pro Leu Asp Phe Leu 10 15

<210> 189 <211> 207 <212> PRT

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<210> 188
<211> 92
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -13..-1
<400> 188
Met Leu Phe Ser Leu Ser Leu Leu Ser Asn Leu Asn Gln Ile Gly Ser
     -10
                           -5
Ser His Leu Asp Arg Pro His Ile Pro Gly Gln Ser Ala Gln Leu Phe
                   10
Ile Tyr Gln Met Ser Ser Gln Gln Leu Gln Gln Gln Pro Ser Ala Asn
                  25
                                     3.0
Lys Lys Ala Gly Lys Ile His Asn Thr Pro Phe Ala Asn Gln Leu Asn
                                  45
Pro Thr Gln His Leu Ala Lys Pro Phe Gln Gln Ile Leu Pro Gly Arg
                              60
Gln Ser Gly Ser Leu Thr Ser Pro Phe Leu Ala Cys
                           75
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<213> Homo sapiens <220> <221> SIGNAL <222> -42..-1 <400> 189 Met His Ile Leu Gln Leu Leu Thr Thr Val Asp Asp Gly Ile Gln Ala -35 -30 Ile Val His Cys Pro Asp Thr Gly Lys Asp Ile Trp Asn Leu Leu Phe -20 -15 Asp Leu Val Cys His Glu Phe Cys Gln Ser Asp Asp Pro Pro Ile Ile -5 Leu Gln Glu Gln Lys Thr Val Leu Ala Ser Val Phe Ser Val Leu Ser 10 15 Ala Ile Tyr Ala Ser Gln Thr Glu Gln Glu Tyr Leu Lys Ile Glu Lys 25 30 Val Asp Leu Pro Leu Ile Asp Ser Leu Ile Arg Val Leu Gln Asn Met 45 Glu Gln Cys Gln Lys Lys Pro Glu Asn Ser Ala Glu Ser Asn Thr Glu 65 60 Glu Thr Lys Arg Thr Asp Leu Thr Gln Asp Asp Leu His Leu Lys Ile 75 80 Leu Lys Asp Ile Leu Cys Glu Phe Leu Ser Asn Ile Phe Gln Ala Leu 90 95 Thr Lys Glu Thr Val Ala Gln Gly Val Lys Glu Gly Gln Leu Ser Lys 110 Gln Lys Cys Ser Ser Ala Phe Gln Asn Leu Leu Pro Phe Tyr Ser Pro 125 130 Val Val Glu Asp Phe Ile Lys Ile Leu Arg Glu Val Asp Lys Ala Leu 135 140 145 Ala Asp Asp Leu Glu Lys Asn Phe Pro Ser Leu Lys Val Gln Thr

<210> 190

and the first of the control of the

155

. 160

165

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<211> 201
<212> PRT
<213> Homo sapiens
<400> 190
Met Gln Val Ala Leu Lys Glu Asp Leu Asp Ala Leu Lys Glu Lys Phe
                                   10
Arg Thr Met Glu Ser Asn Gln Lys Ser Ser Phe Gln Glu Ile Pro Lys
           20
                               25
Leu Asn Glu Glu Leu Leu Ser Lys Gln Lys Gln Leu Glu Lys Ile Glu
                           40
Ser Gly Glu Met Gly Leu Asn Lys Val Trp Ile Asn Ile Thr Glu Met
                       55
Asn Lys Gln Ile Ser Leu Leu Thr Ser Ala Val Asn His Leu Lys Ala
Asn Val Lys Ser Ala Ala Asp Leu Ile Ser Leu Pro Thr Thr Val Glu
                                   90
Gly Leu Gln Lys Ser Val Ala Ser Ile Gly Asn Thr Leu Asn Ser Val
                           105
          100
                                                  110
His Leu Ala Val Glu Ala Leu Gln Lys Thr Val Asp Glu His Lys Lys
      115
                           120
                                               125
Thr Met Glu Leu Leu Gln Ser Asp Met Asn Gln His Phe Leu Lys Glu
                       135
                                           140
Thr Pro Gly Ser Asn Gln Ile Ile Pro Ser Pro Ser Ala Thr Ser Glu
                   150
                                       155
Leu Asp Asn Lys Thr His Ser Glu Asn Leu Lys Gln Met Gly Asp Arg
                                   170
Ser Ala Thr Leu Lys Arg Gln Ser Leu Asp Gln Val Thr Asn Arg Thr
                                185
           180
Asp Thr Val Lys Ile Gln Lys Lys
       195
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<210> 191

<211> 379

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -37..-1

<400> 191

Met Pro His Ser Ser Leu His Pro Ser Ile Pro Cys Pro Arg Gly His

Gly Ala Gln Lys Ala Ala Leu Val Leu Leu Ser Ala Cys Leu Val Thr
-20 -15 -10

Leu Trp Gly Leu Gly Glu Pro Pro Glu His Thr Leu Arg Tyr Leu Val

Leu His Leu Ala Ser Leu Gln Leu Gly Leu Leu Leu Asn Gly Val Cys
15 20 25

Ser Leu Ala Glu Glu Leu Arg His Ile His Ser Arg Tyr Arg Gly Ser 30 35 40

Tyr Trp Arg Thr Val Arg Ala Cys Leu Gly Cys Pro Leu Arg Arg Gly
45 50 55

Ala Leu Leu Leu Ser Ile Tyr Phe Tyr Tyr Ser Leu Pro Asn Ala

de la contrata de la composition della compositi

```
65
                                      70
Val Gly Pro Pro Phe Thr Trp Met Leu Ala Leu Leu Gly Leu Ser Gln
                                  85
Ala Leu Asn Ile Leu Leu Gly Leu Lys Gly Leu Ala Pro Ala Glu Ile
                              100
Ser Ala Val Cys Glu Lys Gly Asn Phe Asn Val Ala His Gly Leu Ala
                          115
Trp Ser Tyr Tyr Ile Gly Tyr Leu Arg Leu Ile Leu Pro Glu Leu Gln
                     130
                                         135
Ala Arg Ile Arg Thr Tyr Asn Gln His Tyr Asn Asn Leu Leu Arg Gly
                  145
                                     150
Ala Val Ser Gln Arg Leu Tyr Ile Leu Leu Pro Leu Asp Cys Gly Val
              160
                                 165
Pro Asp Asn Leu Ser Met Ala Asp Pro Asn Ile Arg Phe Leu Asp Lys
         175
                    180
Leu Pro Gln Gln Thr Gly Asp Arg Ala Gly Ile Lys Asp Arg Val Tyr
       190
                         195
                                            200
Ser Asn Ser Ile Tyr Glu Leu Leu Glu Asn Gly Gln Arg Ala Gly Thr
                       210
                                          215
Cys Val Leu Glu Tyr Ala Thr Pro Leu Gln Thr Leu Phe Ala Met Ser
220
                   225
                                      230
Gln Tyr Ser Gln Ala Gly Phe Ser Arg Glu Asp Arg Leu Glu Gln Ala
             240
                                  245
Lys Leu Phe Cys Arg Thr Leu Glu Asp Ile Leu Ala Asp Ala Pro Glu
           255
                              260
Ser Gln Asn Asn Cys Arg Leu Ile Ala Tyr Gln Glu Pro Ala Asp Asp
                          275
                                              280
Ser Ser Phe Ser Leu Ser Gln Glu Val Leu Arg His Leu Arg Gln Glu
                      290
                                         295
Glu Lys Glu Glu Val Thr Val Gly Ser Leu Lys Thr Ser Ala Val Pro
                 305
                                     310
Ser Thr Ser Thr Met Ser Gln Glu Pro Glu Leu Leu Ser Gly Met
             320
                                 325
Gly Lys Pro Leu Pro Leu Arg Thr Asp Phe Ser
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<210> 192 <211> 112 <212> PRT <213> Homo sapiens

<400> 192 Met Pro Ser Glu Gly Arg Cys Trp Glu Thr Leu Lys Ala Leu Arg Ser 10 Ser Asp Lys Gly Arg Leu Cys Tyr Tyr Arg Asp Trp Leu Leu Arg Arg 25 Glu Asp Val Leu Glu Glu Cys Met Ser Leu Pro Lys Leu Ser Ser Tyr 40 45 Ser Gly Trp Val Val Glu His Val Leu Pro His Met Gln Glu Asn Gln 55 60 Pro Leu Ser Glu Thr Ser Pro Ser Ser Thr Ser Ala Ser Ala Leu Asp 70 75 Gln Pro Ser Phe Val Pro Lys Ser Pro Asp Ala Ser Ser Ala Phe Ser 90 Pro Ala Ser Pro Ala Thr Pro Asn Gly Thr Lys Gly Lys Lys Lys

and the control of th

<211> 43 <212> PRT <213> Homo sapiens

Ser Arg Ile Met Thr His Arg Ser Ala Glu Lys 35 40

<210> 194 <211> 51 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1

Pro Asn Phe 35

<210> 195
<211> 244
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1
<400> 195

Met Ala Asn Pro Lys Leu Leu Gly Leu Glu Leu Ser Glu Ala Glu Ala -10 Ile Gly Ala Asp Ser Ala Arg Phe Glu Glu Leu Leu Gln Ala Ser Lys Glu Leu Gln Gln Ala Gln Thr Thr Arg Pro Glu Ser Thr Gln Ile 25 20 Gln Pro Gln Pro Gly Phe Cys Ile Lys Thr Asn Ser Ser Glu Gly Lys 40 35 Val Phe Ile Asn Ile Cys His Ser Pro Ser Ile Pro Pro Pro Ala Asp 55 Val Thr Glu Glu Glu Leu Leu Gln Met Leu Glu Glu Asp Gln Ala Gly 70 75 Phe Arg Ile Pro Met Ser Leu Gly Glu Pro His Ala Glu Leu Asp Ala 90 85 Lys Gly Gln Gly Cys Thr Ala Tyr Asp Val Ala Val Asn Ser Asp Phe 105 Tyr Arg Arg Met Gln Asn Ser Asp Phe Leu Arg Glu Leu Val Ile Thr provided the following provides the control of the

```
115
                                 120
Ile Ala Arg Glu Gly Leu Glu Asp Ile Tyr Asn Leu Gln Leu Asn Pro
          130
                             135
Glu Trp Arg Met Met Lys Asn Arg Pro Phe Met Gly Ser Ile Ser Gln
       145
                         150
                                            155
Gln Asn Ile Arg Ser Glu Gln Arg Pro Arg Ile Gln Glu Leu Gly Asp
                     165
                                       170
Leu Tyr Thr Pro Ala Pro Gly Arg Ala Glu Ser Gly Pro Glu Lys Pro
               180
                                    185
His Leu Asn Leu Trp Leu Glu Ala Pro Asp Leu Leu Leu Ala Glu Val
           195
                       200
Asp Leu Pro Lys Leu Asp Gly Ala Leu Gly Leu Ser Leu Glu Ile Gly
          210
                             215
Arg Thr Ala Trp
       225
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<210> 196 <211> 353 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -34..-1

<400> 196 Met Glu Arg Gly Leu Lys Ser Ala Asp Pro Arg Asp Gly Thr Gly Tyr -30 -25 -20 Thr Gly Trp Ala Gly Ile Ala Val Leu Tyr Leu His Leu Tyr Asp Val -10 Phe Gly Asp Pro Ala Tyr Leu Gln Leu Ala His Gly Tyr Val Lys Gln 1 5 10 Ser Leu Asn Cys Leu Thr Lys Arg Ser Ile Thr Phe Leu Cys Gly Asp 20 25 Ala Gly Pro Leu Ala Val Ala Ala Val Leu Tyr His Lys Met Asn Asn 35 40 Glu Lys Gln Ala Glu Asp Cys Ile Thr Arg Leu Ile His Leu Asn Lys 55 Ile Asp Pro His Ala Pro Asn Glu Met Leu Tyr Gly Arg Ile Gly Tyr 70 Ile Tyr Ala Leu Leu Phe Val Asn Lys Asn Phe Gly Val Glu Lys Thr 85 Pro Gln Ser His Ile Gln Gln Ile Cys Glu Thr Ile Leu Thr Ser Gly 100 105 Glu Asn Leu Ala Arg Lys Arg Asn Phe Thr Ala Lys Ser Pro Leu Met 115 120 Tyr Glu Trp Tyr Gln Glu Tyr Tyr Val Gly Ala Ala His Gly Leu Ala 130 135 Gly Ile Tyr Tyr Leu Met Gln Pro Ser Leu Gln Val Ser Gln Gly 145 150 155 Lys Leu His Ser Leu Val Lys Pro Ser Val Asp Tyr Val Cys Gln Leu 165 170 Lys Phe Pro Ser Gly Asn Tyr Pro Pro Cys Ile Gly Asp Asn Arg Asp 180 185 Leu Leu Val His Trp Cys His Gly Ala Pro Gly Val Ile Tyr Met Leu 195 200 Ile Gln Ala Tyr Lys Val Phe Arg Glu Glu Lys Tyr Leu Cys Asp Ala 210 215 Tyr Gln Cys Ala Asp Val Ile Trp Gln Tyr Gly Leu Leu Lys Lys Gly

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Tyr Gly Leu Cys His Gly Ser Ala Gly Asn Ala Tyr Ala Phe Leu Thr 245 250 Leu Tyr Asn Leu Thr Gln Asp Met Lys Tyr Leu Tyr Arg Ala Cys Lys 260 265 Phe Ala Glu Trp Cys Leu Glu Tyr Gly Glu His Gly Cys Arg Thr Pro 275 280 Asp Thr Pro Phe Ser Leu Phe Glu Gly Met Ala Gly Thr Ile Tyr Phe 290 295 300 Leu Ala Asp Leu Leu Val Pro Thr Lys Ala Arg Phe Pro Ala Phe Glu 310

Leu

<210> 197 <211> 30 <212> PRT <213> Homo sapiens

<400> 197 Met Gln Met Asp Thr Phe Phe Met Ser Glu Lys His Thr His Thr His 10 5 Thr His Ile His Thr His Thr Arg Lys Thr Lys Lys Lys 25

<210> 198 <211> 112 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -48..-1

<400> 198 Met Gln Asp Thr Gly Ser Val Val Pro Leu His Trp Phe Gly Phe Gly -40 -35 -45 Tyr Ala Ala Leu Val Ala Ser Gly Gly Ile Ile Gly Tyr Val Lys Ala -30 -25 Gly Ser Val Pro Ser Leu Ala Ala Gly Leu Leu Phe Gly Ser Leu Ala -5 -10 Gly Leu Gly Ala Tyr Gln Leu Ser Gln Asp Pro Arg Asn Val Trp Val 10 15 5 . Phe Leu Ala Thr Ser Gly Thr Leu Ala Gly Ile Met Gly Met Arg Phe 25 20 Tyr His Ser Gly Lys Phe Met Pro Ala Gly Leu Ile Ala Gly Ala Ser 40 45 Leu Leu Met Val Ala Lys Val Gly Val Ser Met Phe Asn Arg Pro His

<210> 199 <211> 54 <212> PRT <213> Homo sapiens <400> 199 Glu Ile Ala Gly Tyr Gly Ala Glu Gly Phe Ser Ser Val Leu Gly Tyr Pro Arg Trp His Arg Leu Pro Pro Gln Ser Leu Gln His His Gln Tyr 25 Cys Gln Arg Arg Trp Pro Asp Arg Cys Leu Gln Ser His Thr Gln 40 Ser Ser Gly His Leu Pro

<210> 200 <211> 151 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 200 Met Ala Ala Ser Thr Ser Met Xaa Pro Val Ala Val Thr Ala Ala Val -15 -10 Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile 1 Lys Lys Gln Leu Leu Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu 20 Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala 35 Leu Pro Xaa Gly Gln Leu Gln Pro Pro Pro Pro Ile Thr Glu Glu Asp 50 ..55 Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val 70 65 Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys Asn Ser Lys 80 85 Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val Arg Ala Ile 100 105 Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe Arg Thr Asn 110 115 Gly Lys Val Lys Ser Phe Lys 125

<210> 201 <211> 228 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -25..-1 <400> 201 Met Ser Met Ala Val Glu Thr Phe Gly Phe Phe Met Ala Thr Val Gly -20 -15 Leu Leu Met Leu Gly Val Thr Leu Pro Asn Ser Tyr Trp Arg Val Ser - 5 1 Thr Val His Gly Asn Val Ile Thr Thr Asn Thr Ile Phe Glu Asn Leu

30

45

15

Trp Phe Ser Cys Ala Thr Asp Ser Leu Gly Val Tyr Asn Cys Trp Glu

Phe Pro Ser Met Leu Ala Leu Ser Gly Tyr Ile Gln Ala Cys Arg Ala

-10

20

35

Leu Met Ile Thr Ala Ile Leu Leu Gly Phe Leu Gly Leu Leu Leu Gly 60 Ile Ala Gly Leu Arg Cys Thr Asn Ile Gly Gly Leu Glu Leu Ser Arg 80 Lys Ala Lys Leu Ala Ala Thr Ala Gly Ala Pro His Ile Leu Ala Gly 95 Ile Cys Gly Met Val Ala Ile Ser Trp Tyr Ala Phe Asn Ile Thr Arg 115 110 Asp Phe Phe Asp Pro Leu Tyr Pro Gly Thr Lys Tyr Glu Leu Gly Pro 130 125 Ala Leu Tyr Leu Gly Trp Ser Ala Ser Leu Ile Ser Ile Leu Gly Gly 145 140 Leu Cys Leu Cys Ser Ala Cys Cys Cys Gly Ser Asp Glu Asp Pro Ala 160 155 Ala Ser Ala Arg Arg Pro Tyr Gln Ala Pro Val Ser Val Met Pro Val 175 Ala Thr Ser Asp Gln Glu Gly Asp Ser Ser Phe Gly Lys Tyr Gly Arg 190 Asn Ala Tyr Val 200

<211> 64 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -47..-1 <400> 202 Met His Gly Phe Glu Ile Ile Ser Leu Lys Glu Glu Ser Pro Leu Gly -40 -35 Lys Val Ser Gln Gly Pro Leu Phe Asn Val Thr Ser Gly Ser Ser Ser -20 -25 Pro Val Thr Trp Leu Gly Leu Leu Ser Phe Gln Asn Leu His Cys Phe -5 -10

Pro Val Thr Trp Leu Gly Leu Leu Sel Phe Gli Ash Leu his cys The
-15 -10 -5 1
Pro Asp Leu Pro Thr Glu Met Pro Leu Arg Ala Lys Gly Val Asn Thr
5 10 15

<210> 203 <211> 146 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -31..-1

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<210> 202

And a complete of the control of the control of the control of the first that the control of the

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Gly Pro Pro Leu Asn Ile His Tyr Leu Lys Leu Ile Asp Arg Glu Asn Phe Val Asp Ile Val Asp Ala Lys Leu Lys Ile Pro Val Ser Gly Ser Lys Ser Glu Gly Leu Leu Tyr Val His Ser Ser Arg Gly Gly Pro Phe 70 Gln Arg Trp His Leu Asp Glu Val Phe Leu Glu Leu Lys Asp Gly Gln 90 Gln Ile Pro Val Phe Lys Leu Ser Gly Glu Asn Gly Asp Glu Val Lys 105 Lys Glu 115

<210> 204 <211> 87 <212> PRT <213> Homo sapiens

<400> 204 Met Glu Leu Ala Pro Thr Ala Arg Leu Pro Pro Gly His Gly Ser Leu Pro His Gly Val Leu Gly Pro Arg Ala Thr Gly Ser Val Thr His Leu 20 25 Ser Leu Leu Pro Gln Ile Lys Gln Arg Ala Ser Glu Ala Leu Pro Glu 35 40 45 Leu Leu Arg Pro Val Thr Pro Ile Thr Asn Phe Glu Gly Ser Gln Ser 55 60 Gln Asp His Ser Gly Ile Phe Gly Leu Val Thr Asn Leu Glu Glu Leu 75 70 Glu Val Asp Asp Trp Glu Phe 85

<210> 205 <211> 40 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -27..-1

<400> 205 Met Arg Thr Leu Phe Gly Ala Val Arg Ala Pro Phe Ser Ser Leu Thr -20 Leu Leu Ile Thr Pro Ser Pro Ser Pro Leu Leu Phe Asp Arg Gly -10 - 5 1 Leu Ser Leu Arg Ser Ala Met Ser 10

<210> 206 <211> 154 <212> PRT <213> Homo sapiens

<400> 206 Met Gly Ser Leu Ser Gly Leu Arg Leu Ala Ala Gly Ser Cys Phe Arg to the control of the

10 1 Leu Cys Glu Arg Asp Val Ser Ser Ser Leu Arg Leu Thr Arg Ser Ser 25 30 20 Asp Leu Lys Arg Ile Asn Gly Phe Cys Thr Lys Pro Gln Glu Ser Pro 45 40 35 Gly Ala Pro Ser Arg Thr Tyr Asn Arg Val Pro Leu His Lys Pro Thr 60 55 Asp Trp Gln Lys Lys Ile Leu Ile Trp Ser Gly Arg Phe Lys Lys Glu 75 70 Asp Glu Ile Pro Glu Thr Val Ser Leu Glu Met Leu Asp Ala Ala Lys 90 85 Asn Lys Met Arg Val Lys Ser Ser Tyr Leu Met Ile Ala Leu Thr Val 100 105 Val Gly Cys Ile Phe Met Val Ile Glu Gly Lys Lys Ala Ala Gln Arg 125 120 His Glu Thr Leu Thr Ser Leu Asn Leu Glu Lys Lys Ala Arg Leu Lys 140 135 Glu Glu Ala Ala Met Lys Ala Lys Thr Glu

<210> 207 <211> 101 <212> PRT <213> Homo sapiens

<213> Homo sapiens

<400> 207 Met Val Cys Glu Lys Cys Glu Lys Lys Leu Gly Thr Val Ile Thr Pro 10 Asp Thr Trp Lys Asp Gly Ala Arg Asn Thr Thr Glu Ser Gly Gly Arg 25 20 Lys Leu Asn Lys Asn Lys Ala Leu Thr Ser Lys Lys Ala Arg Phe Asp 40 Pro Tyr Gly Lys Asn Lys Phe Ser Thr Cys Arg Ile Cys Lys Ser Ser 55 Val His Gln Pro Gly Ser His Tyr Cys Gln Gly Cys Ala Tyr Lys Lys 75 70 Gly Ile Cys Ala Met Cys Gly Lys Lys Val Leu Asp Thr Lys Asn Tyr Lys Gln Thr Ser Val . 100

<210> 208 <211> 456 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1

d so a distribution mediane at the most contact and a conflict distribution and accommendation of the distribution of the conflict of the conf

```
35
Glu Glu Glu Glu Glu Arg Lys Lys Cys Pro Lys Lys Ala Ser
                50
Phe Ala Ser Ala Ser Ala Glu Val Gly Lys Lys Lys Lys Cys
                  65
Gln Lys Gln Gly Pro Pro Cys Ser Asp Ser Glu Glu Glu Val Glu Arg
               80
                       85
Lys Lys Cys His Lys Gln Ala Leu Val Gly Ser Asp Ser Ala Glu
                   100
           95
Asp Glu Lys Arg Lys Cys Gln Lys His Ala Pro Ile Asn Ser
        110 115 120
Ala Gln His Leu Asp Asn Val Asp Gln Thr Gly Pro Lys Ala Trp Lys
                             135
            130
Gly Ser Thr Thr Asn Asp Pro Pro Lys Gln Ser Pro Gly Ser Thr Ser
          145
                                   150
Pro Lys Pro Pro His Thr Leu Ser Arg Lys Gln Trp Arg Asn Arg Gln
      160
                               165
Lys Asn Lys Arg Arg Cys Lys Asn Lys Phe Gln Pro Pro Gln Val Pro
            175
                           180
Asp Gln Ala Pro Ala Glu Ala Pro Thr Glu Lys Thr Glu Val Ser Pro
         190
                         195
Val Pro Arg Thr Asp Ser His Gly Ala Arg Ala Gly Ala Leu Arg Ala
                      210
                                      215
Arg Met Ala Gln Arg Leu Asp Gly Ala Arg Phe Arg Tyr Leu Asn Glu
                  225
                                   230
Gln Leu Tyr Ser Gly Pro Ser Ser Ala Ala Gln Arg Leu Phe Gln Glu
               240
                                245
Asp Pro Glu Ala Phe Leu Leu Tyr His Arg Gly Phe Gln Ser Gln Val
            255
                            260
Lys Lys Trp Pro Leu Gln Pro Val Asp Arg Ile Ala Arg Asp Leu Arg
                         275
         270
                                          280
Gln Arg Pro Ala Ser Leu Val Val Ala Asp Phe Gly Cys Gly Asp Cys
                      290
Arg Leu Ala Ser Ser Ile Arg Asn Pro Val His Cys Phe Asp Leu Ala
                  305
                                   310
Ser Leu Asp Pro Arg Val Thr Val Cys Asp Met Ala Gln Val Pro Leu
                                325 330
               320
Glu Asp Glu Ser Val Asp Val Ala Val Phe Cys Leu Ser Leu Met Gly
                            340
         335
Thr Asn Ile Arg Asp Phe Leu Glu Glu Ala Asn Arg Val Leu Lys Pro
                         355
Gly Gly Leu Leu Lys Val Ala Glu Val Ser Ser Arg Phe Glu Asp Val
                      370 375
Arg Thr Phe Leu Arg Ala Val Thr Lys Leu Gly Phe Lys Ile Val Ser
                          390
   380 385
Lys Asp Leu Thr Asn Ser His Phe Phe Leu Phe Asp Phe Gln Lys Thr
      400
                                405
Gly Pro Pro Leu Val Gly Pro Lys Ala Gln Leu Ser Gly Leu Gln Leu
            415
Gln Pro Cys Leu Tyr Lys Arg Arg
          430
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<210> 209 <211> 98 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -17..-1

<400> 209 Met Pro Ser Ser Phe Phe Leu Leu Leu Gln Phe Phe Leu Arg Ile Asp -10 -5 Gly Val Leu Ile Arg Met Asn Asp Thr Arg Leu Tyr His Glu Ala Asp 5 10 Lys Thr Tyr Met Leu Arg Glu Tyr Thr Ser Arg Glu Ser Lys Ile Ser 25 2.0 Ser Leu Met His Val Pro Pro Ser Leu Phe Thr Glu Pro Asn Glu Ile 35 40 Ser Gln Tyr Leu Pro Ile Lys Glu Ala Val Cys Glu Lys Leu Ile Phe 60 55 Pro Glu Arg Ile Asp Pro Asn Pro Ala Asp Ser Gln Lys Ser Thr Gln 70 Val Glu 80

<210> 210 <211> 83 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -29..-1

<210> 211 <211> 229 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -23..-1

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50
          45
Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr
                       65
Val Glu Thr Glu Val Gly Asp Tyr Met Phe Cys Phe Asp Asn Thr Phe
                                     85
                    80
Ser Thr Ile Ser Glu Lys Val Ile Phe Phe Glu Leu Ile Leu Asp Asn
                                  100
                95
Met Gly Glu Gln Ala Gln Glu Gln Glu Asp Trp Lys Lys Tyr Ile Thr
                             115
             110
Gly Thr Asp Ile Leu Asp Met Lys Leu Glu Asp Ile Leu Glu Ser Ile
                                   135
                        130
         125
Ser Ser Ile Lys Ser Arg Leu Ser Lys Ser Gly His Ile Gln Ile Leu
                               150
                145
Leu Arg Ala Phe Glu Ala Arg Asp Arg Asn Ile Gln Glu Ser Asn Phe
                              165
            160
Asp Arg Val Asn Phe Trp Ser Met Val Asn Leu Val Val Met Val Val
                        180
        175
Val Ser Ala Ile Gln Val Tyr Met Leu Lys Ser Leu Phe Glu Asp Lys
           190
                               195
Arg Lys Ser Arg Thr
          205
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<210> 212 <211> 152 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

<400> 212 Met Ala Gln Leu Gly Ala Val Val Ala Val Ala Ser Ser Phe Phe Cys -15 Ala Ser Leu Phe Ser Ala Val His Lys Ile Glu Glu Gly His Ile Gly 1 Val Tyr Tyr Arg Gly Gly Ala Leu Leu Thr Ser Thr Ser Gly Pro Gly 20 Phe His Leu Met Leu Pro Phe Ile Thr Ser Tyr Lys Ser Val Gln Thr 35 40 Thr Leu Gln Thr Asp Glu Val Lys Asn Val Pro Cys Gly Thr Ser Gly 55 50 Gly Val Met Ile Tyr Phe Asp Arg Ile Glu Val Val Asn Phe Leu Val 70 Pro Asn Ala Val His Asp Ile Val Lys Asn Tyr Thr Ala Asp Tyr Asp 85 80 Lys Ala Leu Ile Phe Asn Lys Ile His His Glu Leu Asn Gln Phe Cys 105 100 95 Ser Val His Thr Leu Gln Glu Val Tyr Ile Glu Leu Phe Gly Leu Glu 115 110 Asn Asp Phe Ser Gln Glu Ser Ser 130 125

<210> 213 <211> 179 <212> PRT <213> Home sapiens <220> <221> SIGNAL <222> -54..-1

<400> 213

Met Ala Ala Ser Glu Ala Ala Val Val Ser Ser Pro Ser Leu Lys Thr -45 Asp Thr Ser Pro Val Leu Glu Thr Ala Gly Thr Val Ala Ala Met Ala -30 -35 Ala Thr Pro Ser Ala Arg Ala Ala Ala Ala Val Val Ala Ala Ala Ala -15 -10 Arg Thr Gly Ser Glu Ala Arg Val Ser Lys Ala Ala Leu Ala Thr Lys 1 Leu Leu Ser Leu Ser Gly Val Phe Ala Val His Lys Pro Lys Gly Pro 20 15 Thr Ser Ala Glu Leu Leu Asn Arg Leu Lys Glu Lys Leu Leu Ala Glu 35 Ala Gly Met Pro Ser Pro Glu Trp Thr Lys Arg Lys Lys Gln Thr Leu 50 55 Lys Ile Gly His Gly Gly Thr Leu Asp Ser Ala Ala Arg Gly Val Leu 70 65 Val Val Gly Ile Gly Ser Gly Thr Lys Met Leu Thr Ser Met Leu Ser 80 85 Gly Ser Lys Arg Tyr Thr Ala Ile Gly Glu Leu Gly Lys Ala Thr Asp 95 100 Thr Leu Asp Ser Thr Gly Lys Val Thr Glu Glu Lys Pro Tyr Gly Met

115 Asn Leu Ile

125

<210> 214 <211> 269 <212> PRT <213> Homo sapiens

<220> <221> SIGNAL <222> -92..-1

<400> 214

Met Ile Thr His Val Thr Leu Glu Asp Ala Leu Ser Asn Val Asp Leu -85 Leu Glu Glu Leu Pro Leu Pro Asp Gln Gln Pro Cys Ile Glu Pro Pro -70 -65 Pro Ser Ser Ile Met Tyr Gln Ala Asn Phe Asp Thr Asn Phe Glu Asp -50 -55 Arg Asn Ala Phe Val Thr Gly Ile Ala Arg Tyr Ile Glu Gln Ala Thr -35 -40 Val His Ser Ser Met Asn Glu Met Leu Glu Glu Gly His Glu Tyr Ala -25 -20 Val Met Leu Tyr Thr Trp Arg Ser Cys Ser Arg Ala Ile Pro Gln Val -5 Lys Cys Asn Glu Gln Pro Asn Arg Val Glu Ile Tyr Glu Lys Thr Val 10 15 Glu Val Leu Glu Pro Glu Val Thr Lys Leu Met Lys Phe Met Tyr Phe 30 25 Gln Arg Lys Ala Ile Glu Arg Phe Cys Ser Glu Val Lys Arg Leu Cys 50 45 His Ala Glu Arg Arg Lys Asp Phe Val Ser Glu Ala Tyr Leu Leu Thr

and the first of the first of the contraction of th

Leu Gly Lys Phe Ile Asn Met Phe Ala Val Leu Asp Glu Leu Lys Asn 75 Met Lys Cys Ser Val Lys Asn Asp His Ser Ala Tyr Lys Arg Ala Ala 90 Gln Phe Leu Arg Lys Met Ala Asp Pro Gln Ser Ile Gln Glu Ser Gln 110 105 Asn Leu Ser Met Phe Leu Ala Asn His Asn Arg Ile Thr Gln Cys Leu 125 His Gln Gln Leu Glu Val Ile Pro Gly Tyr Glu Glu Leu Leu Ala Asp 145 140 Ile Val Asn Ile Cys Val Asp Tyr Tyr Glu Asn Lys Met Tyr Leu Thr 150 155 160 Pro Ser Glu Lys His Met Leu Leu Lys Val Lys Leu Pro 170

<211> 135 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1 <400> 215 Met Gln Thr Val Tyr Tyr Gly Ser Leu Gly Leu Trp Leu Ala Leu Val -15 Asp Gly Leu Val Arg Ser Ser Pro Ser Leu Asp Gln Met Phe Asp Ala 1 5 Glu Ile Leu Gly Phe Ser Thr Pro Pro Gly Arg Leu Ser Met Met Ser 20 15 Phe Ile Phe Asn Ala Leu Thr Cys Ala Leu Gly Leu Leu Tyr Phe Ile . 30 35 40 Arg Arg Gly Lys Gln Cys Leu Asp Phe Thr Val Thr Val His Phe Phe 50 His Leu Leu Gly Cys Trp Phe Tyr Ser Ser Arg Phe Pro Ser Ala Leu

Thr Trp Trp Leu Val Gln Ala Val Cys Ile Ala Leu Met Ala Val Ile

Gly Glu Tyr Leu Cys Met Arg Thr Glu Leu Lys Glu Ile Pro Leu Asn

85

100

80

95

Ser Ala Pro Lys Ser Asn Val

-20

<210> 215

Val Lys Gly His Val Lys Met Leu Arg Leu Val Phe Ala Leu Val Thr

-15

<210> 217 <211> 125 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -54..-1 <400> 217 Met Ala Asp Glu Glu Leu Glu Ala Leu Arg Arg Gln Arg Leu Ala Glu -45 -50 Leu Gln Ala Lys His Gly Asp Pro Gly Asp Ala Ala Gln Gln Glu Ala -35 -30 Lys His Arg Glu Ala Glu Met Arg Asn Ser Ile Leu Ala Gln Val Leu -15 -20 Asp Gln Ser Ala Arg Ala Arg Leu Ser Asn Leu Ala Leu Val Lys Pro 5 1 Glu Lys Thr Lys Ala Val Glu Asn Tyr Leu Ile Gln Met Ala Arg Tyr 20 15 Gly Gln Leu Ser Glu Lys Val Ser Glu Gln Gly Leu Ile Glu Ile Leu 35 Lys Lys Val Ser Gln Gln Thr Glu Lys Thr Thr Thr Val Lys Phe Asn

50

Arg Arg Lys Val Met Asp Ser Asp Glu Asp Asp Asp Tyr
60 65 70

<210> 218
<211> 376
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 218

45

Met Gly His Arg Phe Leu Arg Gly Leu Leu Thr Leu Leu Pro Pro -10 -15 Pro Pro Leu Tyr Thr Arg His Arg Met Leu Gly Pro Glu Ser Val Pro Pro Pro Lys Arg Ser Arg Ser Lys Leu Met Ala Pro Pro Arg Ile Gly 20 15 Thr His Asn Gly Thr Phe His Cys Asp Glu Ala Leu Ala Cys Ala Leu 35 Leu Arg Leu Leu Pro Glu Tyr Arg Asp Ala Glu Ile Val Arg Thr Arg 55 50 Asp Pro Glu Lys Leu Ala Ser Cys Asp Ile Val Val Asp Val Gly Gly 70 65 Glu Tyr Asp Pro Arg Arg His Arg Tyr Asp His His Gln Arg Ser Phe 85 Thr Glu Thr Met Ser Ser Leu Ser Pro Gly Arg Pro Trp Gln Thr Lys

```
100
Leu Ser Ser Ala Gly Leu Ile Tyr Leu His Phe Gly His Lys Leu Leu
                        115
                                 120
Ala Gln Leu Leu Gly Thr Ser Glu Glu Asp Ser Met Val Gly Thr Leu
                    130
                                      135
Tyr Asp Lys Met Tyr Glu Asn Phe Val Glu Glu Val Asp Ala Val Asp
                  145
                                     150
Asn Gly Ile Ser Gln Trp Ala Glu Gly Glu Pro Arg Tyr Ala Leu Thr
              160
                                 165
Thr Thr Leu Ser Ala Arg Val Ala Arg Leu Asn Pro Thr Trp Asn His
          175
                             180
Pro Asp Gln Asp Thr Glu Ala Gly Phe Lys Arg Ala Met Asp Leu Val
                         195
                                          200
Gln Glu Glu Phe Leu Gln Arg Leu Asp Phe Tyr Gln His Ser Trp Leu
                     210
                                        215
Pro Ala Arg Ala Leu Val Glu Glu Ala Leu Ala Gln Arg Phe Gln Val
                  225
                                     230
Asp Pro Ser Gly Glu Ile Val Glu Leu Ala Lys Gly Ala Cys Pro Trp
              240
                                 245
Lys Glu His Leu Tyr His Leu Glu Ser Gly Leu Ser Pro Pro Val Ala
           255
                            260
Ile Phe Phe Val Ile Tyr Thr Asp Gln Ala Gly Gln Trp Arg Ile Gln
                         275
                                   280
Cys Val Pro Lys Glu Pro His Ser Phe Gln Ser Arg Leu Pro Leu Pro
                      290
                                        295
Glu Pro Trp Arg Gly Leu Arg Asp Glu Ala Leu Asp Gln Val Ser Gly
                  305
                                     310
Ile Pro Gly Cys Ile Phe Val His Ala Ser Gly Phe Ile Gly Gly His
              320
                                 325 ...
Arg Thr Arg Glu Gly Ala Leu Ser Met Ala Arg Ala Thr Leu Ala Gln
Arg Ser Tyr Leu Pro Gln Ile Ser
       350
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<210> 219 <211> 211 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 219

<222> -30..-1

Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val -25 -20 Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Ala Pro -10 - 5 Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu 10 15 Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu 25 30 Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly 40 45 Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly 55 60 Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Val Pro Arg Met 75 Glu Glu Lys Glu Ala Leu Val Pro Ile Gln Lys Ala Thr Asp Ser Phe 90

Anadous - Santo santo de la missione de la Carabación de Anadous de de Carabación de Carabación de La Carabación de Carabación d

His Thr Glu Leu His Pro Arg Val Ala Phe Trp Ile Ile Lys Leu Pro 105 110 Arg Arg Arg Ser His Gln Asp Ala Leu Glu Gly Gly His Trp Leu Ser 120 125 115 Glu Lys Arg His Arg Leu Gln Ala Ile Arg Asp Gly Leu Arg Lys Gly 135 140 Thr His Lys Asp Val Leu Glu Glu Gly Thr Glu Ser Ser His Ser 155 150 Arg Leu Ser Pro Arg Lys Thr His Leu Leu Tyr Ile Leu Arg Pro Ser 170 165 Arg Gln Leu 180

<210> 220 <211> 154 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -60..-1

<400> 220 Met Gly Ser Lys Cys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu -55 -50 Arg Gln Arg Arg Gln Lys Leu Leu Leu Ala Gln Leu His His Arg Lys -35 .. -30 -40 Arg Val Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu -20 -15 -25 Val Arg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln -10 -5 Cys Trp Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln 10 15 · Ala Leu Leu Arg Val Tyr Val Ile Gln Glu Gln Ala Thr Val Lys Leu 25 30 35 Gln Ser Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met 50 45 40 Cys Asn Ala Leu Cys Leu Phe Gln Val Pro Glu Ser Ser Leu Ala Phe 60 65 Gln Thr Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln 75 Pro Glu Phe His Ile Glu Ile Leu Ser Ile

90

<210> 221 <211> 123 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -42..-1

85 .

<210> 222 <211> 346 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1

<400> 222 Met Ala Met Ala Gln Lys Leu Ser His Leu Leu Pro Ser Leu Arg Gln -10 Val Ile Gln Glu Pro Gln Leu Ser Leu Gln Pro Glu Pro Val Phe Thr 5 Val Asp Arg Ala Glu Val Pro Pro Leu Phe Trp Lys Pro Tyr Ile Tyr 20 25 Ala Gly Tyr Arg Pro Leu His Gln Thr Trp Arg Phe Tyr Phe Arg Thr 35 40 Leu Phe Gln Gln His Asn Glu Ala Val Asn Val Trp Thr His Leu Leu 50 55 Ala Ala Leu Val Leu Leu Arg Leu Ala Leu Phe Val Glu Thr Val 70 Asp Phe Trp Gly Asp Pro His Ala Leu Pro Leu Phe Ile Ile Val Leu 85 Ala Ser Phe Thr Tyr Leu Ser Leu Ser Ala Leu Ala His Leu Leu Gln 100 105 Ala Lys Ser Glu Phe Trp His Tyr Ser Phe Phe Phe Leu Asp Tyr Val 115 120 Gly Val Ala Val Tyr Gln Phe Gly Ser Ala Leu Ala His Phe Tyr Tyr 130 135 Ala Ile Glu Pro Ala Trp His Ala Gln Val Gln Ala Val Phe Leu Pro 145 150 Met Ala Ala Phe Leu Ala Trp Leu Ser Cys Ile Gly Ser Cys Tyr Asn 165 Lys Tyr Ile Gln Lys Pro Gly Leu Leu Gly Arg Thr Cys Gln Glu Val 175 180 185 Pro Ser Val Leu Ala Tyr Ala Leu Asp Ile Ser Pro Val Val His Arg 195 200 Ile Phe Val Ser Ser Asp Pro Thr Thr Asp Asp Pro Ala Leu Leu Tyr 215 His Lys Cys Gln Val Val Phe Phe Leu Leu Ala Ala Phe Phe Ser 225 230 Thr Phe Met Pro Glu Arg Trp Phe Pro Gly Ser Cys His Val Phe Gly 245 250 Gln Gly His Gln Leu Phe His Ile Phe Leu Val Leu Cys Thr Leu Ala 260 265 Gln Leu Glu Ala Val Ala Leu Asp Tyr Glu Ala Arg Arg Pro Ile Tyr

<210> 223 <211> 210 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -20..-1 Met Asp Asn Arg Phe Ala Thr Ala Phe Val Ile Ala Cys Val Leu Ser -10 -15 Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys 15 20 Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Leu Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Arg Arg 50 55 Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg 70 65 Thr Glu Ser Phe Asp Val Val Thr Lys Cys Val Ser Phe Thr Leu Thr 85 Glu Gln Phe Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly 100 Ile Asp Leu Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro 120 115 Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys 130 135 Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu 150 145 His Leu Leu Ala Val Thr Lys Glu Ser Met Leu Pro Ala Gly Ala Glu 160 165 170 Ser Lys His Thr Ala Thr Pro Ala His Ala Cys Val Gln Thr Gly Lys Pro Lys 190

<210> 224 <211> 184 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -20..-1

<400> 224

Met Asp Asn Arg Phe Ala Thr Ala Phe Val Ile Ala Cys Val Leu Ser

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- 15
                                    - 10
Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp
Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys
                           20
Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr
                      35
Asn Asp Ala Pro Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Arg Arg
                  50
                                      55
Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg
                                   70
Thr Glu Ser Phe Asp Val Val Thr Lys Cys Val Ser Phe Thr Leu Thr
                               85
Glu Gln Phe Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly
                           100
Ile Asp Leu Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro
                       115
                                           120
Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys
                   130
                                       135
Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu
               145
                                   150
His Leu Leu Ala Asp Thr Met Leu
            160
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<210> 225 <211> 227 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 225

<222> -22..-1

Met Gly Trp Thr Met Arg Leu Val Thr Ala Ala Leu Leu Leu Gly Leu -15 Met Met Val Val Thr Gly Asp Glu Asp Glu Asn Ser Pro Cys Ala His Glu Ala Leu Leu Asp Glu Asp Thr Leu Phe Cys Gln Gly Leu Glu Val 20 Phe Tyr Pro Glu Leu Gly Asn Ile Gly Cys Lys Val Val Pro Asp Cys 35 Asn Asn Tyr Arg Gln Lys Ile Thr Ser Trp Met Glu Pro Ile Val Lys 50 Phe Pro Gly Ala Val Asp Gly Ala Thr Tyr Ile Leu Val Met Val Asp Pro Asp Ala Pro Ser Arg Ala Glu Pro Arg Gln Arg Phe Trp Arg His 80 85 Trp Leu Val Thr Asp Ile Lys Gly Ala Asp Leu Lys Lys Gly Lys Ile 100 Gln Gly Gln Glu Leu Ser Ala Tyr Gln Ala Pro Ser Pro Pro Ala His 115 Ser Gly Phe His Arg Tyr Gln Phe Phe Val Tyr Leu Gln Glu Gly Lys 130 Val Ile Ser Leu Leu Pro Lys Glu Asn Lys Thr Arg Gly Ser Trp Lys 145 150 Met Asp Arg Phe Leu Asn Arg Phe His Leu Gly Glu Pro Glu Ala Ser 160 165 Thr Gln Phe Met Thr Gln Asn Tyr Gln Asp Ser Pro Thr Leu Gln Ala 175 180

Pro Arg Glu Arg Ala Ser Glu Pro Lys His Lys Asn Gln Ala Glu Ile
190 195 200

Ala Ala Cys
205

<211> 74 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -41..-1 <400> 226 Met Ile Ala Arg Arg Asn Pro Val Pro Leu Arg Phe Leu Pro Asp Glu -30 -35 Ala Arg Ser Leu Pro Pro Pro Lys Leu Thr Asp Pro Arg Leu Leu Tyr -15 -20 Ile Gly Phe Leu Gly Tyr Cys Ser Gly Leu Ile Asp Asn Leu Ile Arg 1 ~5 Arg Arg Pro Ile Ala Thr Ala Gly Leu His Arg Gln Leu Leu Tyr Ile 15 Thr Ala Phe Phe Leu Leu Asp Ile Ile Leu

<210> 227 <211> 73 <212> PRT <213> Homo sapiens

-400> 227

<210> 226

 Met
 Glu
 Lys
 Tyr
 Glu
 Asn
 Leu
 Gly
 Leu
 Val
 Gly
 Gly
 Gly
 Gly
 Is
 Tyr
 Gly

 Met
 Val
 Met
 Lys
 Cys
 Arg
 Asn
 Lys
 Asp
 Thr
 Gly
 Arg
 Ile
 Val
 Ala
 Ile

 Lys
 Lys
 Phe
 Leu
 Glu
 Ser
 Asp
 Asp
 Asp
 Lys
 Met
 Val
 Lys
 Lys
 Ile
 Ala

 Met
 Arg
 Glu
 Val
 Lys
 Leu
 Leu
 Lys
 Glu
 Leu
 Val
 Asp
 Asp

<210> 228
<211> 82
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1

<210> 229

<211> 119 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -56..-1 <400> 229 Met Ala Glu Pro Ser Ala Ala Thr Gln Ser His Ser Ile Ser Ser -50 Ser Phe Gly Ala Glu Pro Ser Ala Pro Gly Gly Gly Ser Pro Gly -35 -30 -25 Ala Cys Pro Ala Leu Gly Thr Lys Ser Cys Ser Ser Ser Cys Ala Asp -15 Ser Phe Val Ser Ser Ser Ser Gln Pro Val Ser Leu Phe Ser Thr -5 1 Ser Gln Glu Gly Leu Ser Ser Leu Cys Ser Asp Glu Pro Ser Ser Glu 15 20 Ile Met Thr Ser Ser Phe Leu Ser Ser Ser Glu Ile His Asn Thr Gly 30 35 Leu Thr Ile Leu His Gly Glu Lys Ser His Val Leu Gly Ser Gln Pro

<210> 230
<211> 54
<212> PRT
<213> Homo sapiens
<400> 230
Ala Phe Val Trp Glu Pro Ala Met Val Arg Ile Asn Ala Leu Thr Ala

45

Ile Leu Ala Lys Lys Lys Lys 60

Ala Ser Glu Ala Ala Cys Leu Ile Val Ser Val Asp Glu Thr Ile Lys

20

25

Asn Pro Arg Ser Thr Val Asp Ala Pro Thr Ala Ala Gly Arg Gly Arg

35

40

45

Gly Arg Gly Arg Pro His

50

<210> 231 <211> 210 <212> PRT <213> Homo sapiens

175

190

<220>
<221> SIGNAL
<222> -14..-1

<400> 231

Met Leu Thr Leu Leu Gly Leu Ser Phe Ile Leu Ala Gly Leu Ile Val -10 -5 1 Gly Gly Ala Cys Ile Tyr Lys Tyr Phe Met Pro Lys Ser Thr Ile Tyr 10 Arg Gly Glu Met Cys Phe Phe Asp Ser Glu Asp Pro Ala Asn Ser Leu 30 25 Arg Gly Gly Glu Pro Asn Phe Leu Pro Val Thr Glu Glu Ala Asp Ile 45 40 Arg Glu Asp Asp Asn Ile Ala Ile Ile Asp Val Pro Val Pro Ser Phe 55 60 Ser Asp Ser Asp Pro Ala Ala Ile Ile His Asp Phe Glu Lys Gly Met 80 75 Thr Ala Tyr Leu Asp Leu Leu Gly Ile Cys Tyr Leu Met Pro Leu 90 Asn Thr Ser Ile Val Met Pro Pro Lys Asn Leu Val Glu Leu Phe Gly 105 110 Lys Leu Ala Ser Gly Arg Tyr Leu Pro Gln Thr Tyr Val Val Arg Glu 125 120 115 Asp Leu Val Ala Val Glu Glu Ile Arg Asp Val Ser Asn Leu Gly Ile 140 135 Phe Ile Tyr Gln Leu Cys Asn Asn Arg Lys Ser Phe Arg Leu Arg Arg 155 Arg Asp Leu Leu Gly Phe Asn Lys Arg Ala Ile Asp Lys Cys Trp

Lys Ile Arg His Phe Pro Asn Glu Phe Ile Val Glu Thr Lys Ile Cys

<210> 232 <211> 108 <212> PRT <213> Homo sapiens

165 , 170

185

<400> 232

Gln Glu 195

Met Gly Cys Val Phe Gln Ser Thr Glu Asp Lys Cys Ile Phe Lys Ile Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu 25 Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg 35 40 45 Val His Leu Met Gly Asp Ile Leu Cys Asn Asp Gly Ser Leu Leu 55 60 Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg **7**5 70 Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val 90 Leu Pro Glu Glu Pro Lys Gly Thr Gln Met Leu Thr 100

<210> 233 <211> 43

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<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1
<400> 233
Met Ser Ser Gly Arg Leu Arg Trp Leu Met Pro Val Ile Pro Ala Leu
    · -15
Trp Gly Ala Glu Lys Gly Glu Ser Pro Glu Val Ser Ser Phe Glu Thr
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5 Arg Leu Ala Asn Met Ala Lys Pro Cys Leu Tyr

<210> 234 <211> 36 <212> PRT <213> Homo sapiens

<400> 234 Met Ser Ala Arg Ile Pro Phe Tyr Lys Asp Thr Ser Gln Ile Arg Leu 10 Gly Ser Thr Ile Ile Pro His Phe Asn Leu Ile Thr Phe Val Lys Thr 25 Phe Phe Gln Ile 35

-10

<210> 235 <211> 307 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1 <400> 235

Met Leu Ala Val Ser Leu Thr Val Pro Leu Leu Gly Ala Met Met Leu -10 . -5 Leu Glu Ser Pro Ile Asp Pro Gln Pro Leu Ser Phe Lys Glu Pro Pro 10 15 Leu Leu Gly Val Leu His Pro Asn Thr Lys Leu Arg Gln Ala Glu 25 30 Arg Leu Phe Glu Asn Gln Leu Val Gly Pro Glu Ser Ile Ala His Ile 40 45 Gly Asp Val Met Phe Thr Gly Thr Ala Asp Gly Arg Val Val Lys Leu 60 Glu Asn Gly Glu Ile Glu Thr Ile Ala Arg Phe Gly Ser Gly Pro Cys 75 Lys Thr Arg Asp Asp Glu Pro Val Cys Gly Arg Pro Leu Gly Ile Arg 90 95 Ala Gly Pro Asn Gly Thr Leu Phe Val Ala Asp Ala Cys Lys Gly Leu 105 110 Phe Glu Val Asn Pro Trp Lys Arg Glu Val Lys Leu Leu Ser Ser 120 125 Glu Thr Pro Ile Glu Gly Lys Asn Met Ser Phe Val Asn Asp Leu Thr 140

Val Ser Gln Asp Gly Arg Lys Ile Tyr Phe Thr Asp Ser Ser Ser Lys 155 Trp Gln Arg Arg Asp Tyr Leu Leu Val Met Glu Gly Thr Asp Asp 170 175 Gly Arg Leu Leu Glu Tyr Asp Thr Val Thr Arg Glu Val Lys Val Leu 180 185 190 Leu Asp Gln Leu Arg Phe Pro Asn Gly Val Gln Leu Ser Pro Ala Glu 200 205 Asp Phe Val Leu Val Ala Glu Thr Thr Met Ala Arg Ile Arg Arg Val 220 225 Tyr Val Ser Gly Leu Met Lys Gly Gly Ala Asp Leu Phe Val Glu Asn 230 235 Met Pro Gly Phe Pro Asp Asn Ile Arg Pro Ser Ser Ser Gly Gly Tyr 245 250 255 Trp Val Gly Met Ser Thr Ile Arg Pro Asn Pro Gly Phe Ser Met Leu 265 270 Asp Phe Leu Ser Glu Arg Pro Trp Ile Lys Arg Met Ile Phe Lys Ala 285 Lys Lys Lys

<210> 236 <211> 106 <212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -32..-1

<400> 236

Met Phe Ala Pro Ala Val Met Arg Ala Phe Arg Lys Asn Lys Thr Leu -30 -25 -20 Gly Tyr Gly Val Pro Met Leu Leu Leu Ile Val Gly Gly Ser Phe Gly -15 -10 -5 Leu Arg Glu Phe Ser Gln Ile Arg Tyr Asp Ala Val Lys Ser Lys Met 10 Asp Pro Glu Leu Glu Lys Lys Leu Lys Glu Asn Lys Ile Ser Leu Glu 20 25 30 Ser Glu Tyr Glu Lys Ile Lys Asp Ser Lys Phe Asp Asp Trp Lys Asn 40 45 Ile Arg Gly Pro Arg Pro Trp Glu Asp Pro Asp Leu Leu Gln Gly Arg 55 Asn Pro Glu Ser Leu Lys Thr Lys Thr Thr 70

<210> 237 <211> 42 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1

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1
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 Gln Leu Ser Asp Lys Val His Asn Asp Ile
                        20
 <210> 238
 <211> 117
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -20..-1
<400> 238
Met Asp Asn Arg Phe Ala Thr Ala Phe Val Ile Ala Cys Val Leu Ser
                    -15
                                        -10
Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp
                1
Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys
        15
                           20
                                              25
Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr
                       35
Asn Asp Ala Leu Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Gly Arg
                                    _ . . 55
Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg
                65
                                    70
Thr Gly Ile Ser Leu Ile Leu Thr Ser Val Phe Phe Thr Trp Leu Ile
           80
                              85
Ile Asp Lys Thr Thr
        95
<210> 239
<211> 178
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -37..-1
<400> 239
Met Glu Arg Gln Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln Phe
       -35
                            -30
                                               -25
Gln His Xaa Xaa Ala Xaa Xaa Leu Leu Val Phe Asn Phe Leu Leu Ile
    -20
                        -15
                                           -10
Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg Phe Arg Phe
                   1
                                  5
Leu His Glu Thr Gly Gly Ala Met Val Tyr Gly Leu Ile Met Gly Leu
                                20
Ile Ser Arg Tyr Ala Thr Ala Pro Thr Asp Ile Glu Ser Gly Thr Val
       30
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 11e
 Ser Arg Tyr Ala Thr Ala Pro Thr Asp Ile Glu Ser Gly Thr Val 30

 20
 35
 40

 20
 Cys Asp Cys Val Lys Leu Thr Phe Ser Pro Pro Thr Leu Leu Val Asn 45

 30
 50
 55

 45
 50
 55

 Val Thr Asp Gln Val Tyr Glu Tyr Lys Tyr Lys Arg Glu Ile Ser Gln 60
 65
 70

 His Asn Ile Asn Pro His Gln Gly Asn Ala Ile Leu Glu Lys Met Thr 80
 85
 90

 Phe Asp Pro Glu Ile Phe Phe Asn Val Leu Leu Pro Pro Ile Ile Phe

```
100
                                              105
          95
His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly
              115
                                   120
Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val
 125
                     130
                                       135
Ile Gly
140
<210> 240
<211> 126
<212> PRT
<213> Homo sapiens
<220>
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<222> -27..-1
<400> 240
Met Gln Phe Val Asn Val Gly Tyr Phe Leu Ile Ala Ala Gly Val Val
   -25 -20
Val Leu Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr Glu Ser
                                       1 5
 -10
                    -5
Met Cys Ala Leu Val Thr Phe Phe Phe Ile Leu Leu Ile Phe Ile
           10
                                15
Ala Glu Val Ala Ala Ala Val Val Ala Leu Val Tyr Thr Thr Met Ala
                            30
Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys Asp Tyr
                        45
                                          50
Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met Lys Gly
                                      65
                    60
Leu Lys Cys Arg Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp Ser Pro
                                 80
                 75
Tyr Phe Lys Met His Lys Pro Val Thr Met Lys Lys Lys
<210> 241
<211> 174
<212> PRT
<213> Homo sapiens
<220>
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<222> -115..-1
<400> 241
Met Arg Trp Ser Cys Glu His Leu Val Met Val Trp Ile Asn Ala Phe
         -110 -105
Val Met Leu Thr Thr Gln Leu Leu Pro Ser Lys Tyr Cys Asp Leu Leu
                                -90
            - 95
His Lys Ser Ala Ala His Leu Gly Lys Trp Gln Lys Leu Glu His Gly
                           -75
Ser Tyr Ser Asn Ala Pro Gln His Ile Trp Ser Glu Asn Thr Ile Trp
                 -60
Pro Gln Gly Val Leu Val Arg His Ser Arg Cys Leu Tyr Arg Ala Met
          -45
                             -40
Gly Pro Tyr Asn Val Ala Val Pro Ser Asp Val Ser His Ala Arg Phe
```

-30

Tyr Phe Leu Phe His Arg Pro Leu Arg Leu Leu Asn Leu Leu Ile Leu

-25

-10

Ile Glu Gly Gly Val Val Phe Tyr Gln Leu Tyr Ser Leu Leu Arg Ser

Glu Lys Trp Asn His Thr Leu Ser Met Ala Leu Ile Leu Phe Cys Asn

5

-15

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15
                        20
                                             25
Tyr Tyr Val Leu Phe Lys Leu Leu Arg Asp Arg Ile Val Leu Gly Arg
                    35
                                         40
Ala Tyr Ser Tyr Pro Leu Asn Ser Tyr Glu Leu Lys Ala Asn
                50
                                     55
<210> 242
<211> 896
<212> DNA
<213> Homo sapiens
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<221> CDS
<222> 18..173
<221> sig_peptide
<222> 18..77
<223> Von Heijne matrix
      score 6.5
      seq GLCVLQLTTAVTS/AF
<221> polyA_signal
<222> 864..869
<221> polyA_site
<222> 882..893
<400> 242
aadcttcaca gtgtgag atg cct agt gtg aac agt gct gga tta tgt gtc
                                                                       50
                   Met Pro Ser Val Asn Ser Ala Gly Leu Cys Val
                   -20
                                       -15
ttg cag ttg aca acg gca gtr acc agt gcc ttt tta cta gca aaa gtg
                                                                       98
Leu Gln Leu Thr Thr Ala Val Thr Ser Ala Phe Leu Leu Ala Lys Val
                -5
aat cct ttc gaa rct ttt ctc tca agg ggc ttt tgg cta tgt gct gcc
                                                                      146
Asn Pro Phe Glu Xaa Phe Leu Ser Arg Gly Phe Trp Leu Cys Ala Ala
                            15
cat cat ttc att cat cct tgc ctg gat tgagacgtgt tcctgattca
                                                                      193
His His Phe Ile His Pro Cys Leu Asp
aagtgttacc tcaagaagca gaagaagaaa acagactcct gatagttcag gatgcttcag
                                                                      253
agagggcagc acttatacct ggtggtcttt ctgatggtca gttttattcc cctcctgaat
                                                                      313
ccgaagcagg atctgaagaa gctgaagaaa aacaggacag tgagaaacca cttttagaac
                                                                      373
tatgagtact acttttgtta aatgtgaaaa accctcacag aaagtcatcg aggcaaaaag
                                                                      433
aggcaggcag tggagtetee etgtegacag taaagttgaa atggtgaegt eeactgetgg
                                                                      493
ctttattgaa cagctaataa agatttattt attgtaatac ctcacagacg ttgtaccata
tecatgeaca titagttgee tgeetgtgge tggtaaggta atgteatgat teatectete
ttcagtgaga ctgagcctga tgtgttaaca aataggtgaa gaaagtcttg tgctgtattc
                                                                      673
ctaatcaaaa gacttaatat attgaagtaa cactttttta gtaagcaaga taccttttta
                                                                      733
tttcaattca cagaatggaa tttttttgtt tcatgtctca gatttatttt gtatttcttt
                                                                      793
tttaacactc tacatttccc ttgtttttta actcatgcac atgtgctctt tgtacagttt
                                                                      853
taaaaagtgt aataaaatct gacatgtcaa araaaaaaaa mcy
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<211> 851
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 17..595
<221> sig_peptide
<222> 17..85
<223> Von Heijne matrix
      score 3.70000004768372
      seq FLPPLXRAFACRG/CQ
<221> polyA signal
<222> 820..825
<221> polyA site
<222> 840..851
<400> 243
aagggggcgt ggggcc atg gtg gtc ttg cgg gcg ggg aag aac ttt ctc
                                                                       52
                  Met Val Val Leu Arg Ala Gly Lys Lys Thr Phe Leu
                              -20
                                                  -15
ccc cct ctm wgc cgc gcc ttc gcc tgc cgc ggc tgt caa ctc gct ccg
                                                                      100
Pro Pro Leu Xaa Arg Ala Phe Ala Cys Arg Gly Cys Gln Leu Ala Pro
gag ege gge gee gag ege agg gat aca geg eee age ggg gte tea aga
Glu Arg Gly Ala Glu Arg Arg Asp Thr Ala Pro Ser Gly Val Ser Arg
                10
ttc tgc cct cca aga aag tct tgc cat gat tgg ata gga ccc cca gat
                                                                      196
Phe Cys Pro Pro Arg Lys Ser Cys His Asp Trp Ile Gly Pro Pro Asp
                                30
aaa tat tca aac ctt cga cct gtt cac ttt tac ata cct gaa aat gaa
                                                                      244
Lys Tyr Ser Asn Leu Arg Pro Val His Phe Tyr Ile Pro Glu Asn Glu
                            45
tct cca ttg gaa caa aag ctt aga aaa tta aga caa gaa aca caa gaa
                                                                      292
Ser Pro Leu Glu Gln Lys Leu Arg Lys Leu Arg Gln Glu Thr Gln Glu
                        60
                                            65
tgg aat caa cag ttc tgg gca aac cag aat ttg act ttt agt aag gaa
                                                                      340
Trp Asn Gln Gln Phe Trp Ala Asn Gln Asn Leu Thr Phe Ser Lys Glu
                    75
                                        80
aaa gaa gaa ttt att cac tca aga cta aaa act aaa ggc ctg ggc ctg
                                                                      388
Lys Glu Glu Phe Ile His Ser Arg Leu Lys Thr Lys Gly Leu Gly Leu
aga act gaa tca ggt cag aaa gca aca ttg aat gca gaa gaa atg gcg
                                                                      436
Arg Thr Glu Ser Gly Gln Lys Ala Thr Leu Asn Ala Glu Glu Met Ala
            105
                                110
gac ttc tac aag gaa ttt tta agt aaa aat ttt cag aag cac atg tat
                                                                      484
Asp Phe Tyr Lys Glu Phe Leu Ser Lys Asn Phe Gln Lys His Met Tyr
        120
                            125
                                                130
tat aac aga gat tgg tac aag cgc aat ttt gcc atc acc ttc ttc atg
                                                                      532
Tyr Asn Arg Asp Trp Tyr Lys Arg Asn Phe Ala Ile Thr Phe Phe Met
                        140
                                            145
gga aaa gtg gcc ctg gaa agg att tgg aac aag ctt aaa cag aaa caa
                                                                      580
Gly Lys Val Ala Leu Glu Arg Ile Trp Asn Lys Leu Lys Gln Lys Gln
                    155
                                        160
aag aag agg agc aac taggagtcca ctctgaccca gccagagtcc aggtttccac
                                                                      635
Lys Lys Arg Ser Asn
aggaagcara tggagctcct ttcacagggg ctctgagaaa aactggagct gatctcaaga
                                                                      695
agccccacat cttcctaagg ggccccatgg cctgtttggg ggcagggtag gtcctggggc
                                                                      755
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<221> sig_peptide

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actgtgggcc gcctgcctgc tgatgtgggc tctaggccag cttgttgtca cgtacgtggt
                                                                        815
 gtgaaataaa gcccaagcac tgggaaaaaa aaaaaa
                                                                        851
 <210> 244
 <211> 495
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> CDS
 <222> 89..334
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 <222> 89..130
 <223> Von Heijne matrix
       score 3.59999990463257
       seq AFTLXSLLQAALL/CV
 <221> polyA_signal
 <222> 462..467
 <221> polyA_site
 <222> 484..495
 <400> 244
agtaggaasg cgccgsccgt ggaggcgcca cgtcccttgc sgcggcggga gagamatcgc
                                                                        60
ttggacttcg gggcggcctc ggacggcc atg gcc ttt acc ctg tas tca ctg
                                                                       112
                                Met Ala Phe Thr Leu Xaa Ser Leu
                                                -10
ctg cag gca gcc ctg ctc tgc gtc aac gcc atc gca gtg ctg cac gag
                                                                       160
Leu Gln Ala Ala Leu Leu Cys Val Asn Ala Ile Ala Val Leu His Glu
gag cga ttc ctc aag aac att ggc tgg gga aca gac cag gga att ggt
                                                                      208
Glu Arg Phe Leu Lys Asn Ile Gly Trp Gly Thr Asp Gln Gly Ile Gly
                15
                                     20
gga ttt gga gaa gag ccg gga att aaa tca sag sta atg avs ctt att
                                                                      256
Gly Phe Gly Glu Glu Pro Gly Ile Lys Ser Xaa Xaa Met Xaa Leu Ile
                                 35
cga tct gta aga acc gtg atg aga gtg cca ttg ata ata gta aac tca
                                                                      304
Arg Ser Val Arg Thr Val Met Arg Val Pro Leu Ile Ile Val Asn Ser
                            50
att gca att gtg tta ctt tta tta ttt gga tgaatwtcat tggagaaaat
                                                                      354
Ile Ala Ile Val Leu Leu Leu Phe Gly
                        65
ggakactcag aaraggacat gccaktaraa kttattactt tggtcattat tggaatattt
atatettage tggetgacet tgeacttgte aaaaatgtaa agetgaaaat aaaaceaggg
                                                                      474
tttctattta aaaaaaaaa a
                                                                      495
<210> 245
<211> 884
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<213> Homo sapiens
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                                                                       114
                                      Met Asp Lys Leu Lys Lys Val
                                      -55
ctg agc ggg cag gac acg gag gac cgg agc ggc ctg tcc gag gtt gtt
                                                                      162
Leu Ser Gly Gln Asp Thr Glu Asp Arg Ser Gly Leu Ser Glu Val Val
            -45
                                 -40
gag gca tct tca tta agc tgg agt acc agg ata aaa ggc ttc att gcg
                                                                      210
Glu Ala Ser Ser Leu Ser Trp Ser Thr Arg Ile Lys Gly Phe Ile Ala
                            -25
                                                 -20
tgt ttt gct ata gga att ctc tgc tca ctg ctg ggt act gtt ctg ctg
                                                                      258
Cys Phe Ala Ile Gly Ile Leu Cys Ser Leu Leu Gly Thr Val Leu Leu
                         -10
                                             -5
tgg gtg ccc agg aag gga cta cac ctc ttc gca gtg ttt tat acc ttt
                                                                      306
Trp Val Pro Arg Lys Gly Leu His Leu Phe Ala Val Phe Tyr Thr Phe
                                    10
ggt aat atc gca tca att ggg agt acc atc ttc ctc atg gga cca gtg
                                                                      354
Gly Asn Ile Ala Ser Ile Gly Ser Thr Ile Phe Leu Met Gly Pro Val
                                 25
aaa cag ctg aag cga atg ttt gag cct act cgt ttg att gca act atc
                                                                      402
Lys Gln Leu Lys Arg Met Phe Glu Pro Thr Arg Leu Ile Ala Thr Ile
        35
                            40
                                                 45
atg gtg ctg ttg tgt ttt gca ctt acc ctg tgt tct gcc ttt tgg tgg
                                                                      450
Met Val Leu Leu Cys Phe Ala Leu Thr Leu Cys Ser Ala Phe Trp Trp
                        55
cat aac aag gga ctt gca ctt atc ttc tgc att ttg cag tct ttg gca
                                                                      498
His Asn Lys Gly Leu Ala Leu Ile Phe Cys Ile Leu Gln Ser Leu Ala
                    70
                                        75
ttg acg tgg tac agc ctt tcc ttc ata cca ttt gca agg gat gct gtg
                                                                      546
Leu Thr Trp Tyr Ser Leu Ser Phe Ile Pro Phe Ala Arg Asp Ala Val
                85
aaa aad tgt ttt gcc gtg tgt ctt gca taattcatgg ccagttttat
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Lys Xaa Cys Phe Ala Val Cys Leu Ala
            100
gaagetttgg aaggeactat ggacagaage tggtggacag ttttgtwact atettegaaa
                                                                      653
cctctgtctt acagacatgt gccttttatc ttgcagcaat gtgttgcttg tgattcgaac
                                                                      713
atttgagggt tacttttgga agcaacaata cattctcgaa cctgaatgtc agtagcacag
                                                                      773
gatgagaagt gggttctgta tcttgtggag tggaatcttc ctcatgtacc tgtttcctct
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                                                                  109
              Met Lys Ala Leu Cys Leu Leu Leu Pro Val Leu
                          -15
ggg ctg ttg gtg tct agc aag acc ctg tgc tcc atg gaa gaa gcc atc
                                                                  157
Gly Leu Leu Val Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile
                      1
                                      5
aat gag agg atc cag gag gtc gcc ggc tcc cta ata ttt agg gca ata
                                                                  205
Asn Glu Arg Ile Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile
                                  20
               15
age age att gge ega ggg age gag age gte ace tee agg ggg gae etg
                                                                  253
Ser Ser Ile Gly Arg Gly Ser Glu Ser Val Thr Ser Arg Gly Asp Leu
                              35
                                                                  301
get act tgc ccc cga ggc ttc gcc gtc acc ggc tgc act tgt ggc tcc
Ala Thr Cys Pro Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser
                           50
                                                                  349
gcc tgt ggc tcg tgg gat gtg cgc gcc gag acc aca tgt cac tgc cag
Ala Cys Gly Ser Trp Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln
                       65
tgc gcg ggc atg gac tgg acc gga gcg cgc tgc tgt cgt gtg cag ccc
                                                                  397
Cys Ala Gly Met Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro
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ggtacgcgtt gctatacaga atctttggat atgtgcatca gtggtttatg ccaaattgtt

ggctgcgatc accagctggg aagcaccgtc aaggaarata actgtggggt ctg	caacrga 331
natgggtcca cctgccggct ggtccgaggg cartataaat cccakctctc cgc	
torgatgata otgtggttgo aattooctat ggaagtakao atattogoot tgt	cttaaaa 451
ggtcctgatc acttatatct ggaarccawa accctccagg ggactaawgg tga	
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gccaggtcag tcaaatttgc tagttcattt gtcataaaca taactcaagt tcc	aaatagg 931
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tgg tcg cag ctg tgc tgt tca tca cag gca tca tca tcc tca cca gtg Trp Ser Gln Leu Cys Cys Ser Ser Gln Ala Ser Ser Ser Pro Val 130 135 140	536
gca agt gca ggc agc tgt ccc ggt tat gcc gga atc att gca ggt gag Ala Ser Ala Gly Ser Cys Pro Gly Tyr Ala Gly Ile Ile Ala Gly Glu 145 150 155	584
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Pro Gly Leu Xaa Gly Ala Thr Pro Ala Arg Ser Pro Gln Gly Lys Glu 35 40 45	245
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65 70 75 80	200
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Thr Gly Leu His Ser Cys Xaa Asp Gly Met Ala Ser Leu Glu Gly Thr 100 105 110	
cca gct tca gtc ctg gct gat gct tgc cca gga ttc cat gat gtg aan	485
Pro Ala Ser Val Leu Ala Asp Ala Cys Pro Gly Phe His Asp Val Xaa 115 120 125	
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Val Gln Xaa Ala Leu Phe Gly Leu Ser Gly Xaa Xaa Leu Trp Leu Lys 130 135 140	
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45 50 55 60	
gct gtc agt ctg acc aag ctc gtc cgg ggg agg aaa gcc cct ttc cct	501
Ala Val Ser Leu Thr Lys Leu Val Arg Gly Arg Lys Ala Pro Phe Pro	
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Val Gly Asp Ser Gly Ser Gly Arg Gly Leu Gln Pro Ser Pro Gly Cys 80 85 90	
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Tyr Arg Tyr	
95	
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Clin Pro Thr Cys Leu Trp Phe Arg Tyr Gly Ala His Gln Pro Glu Asn 35
Step
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Leu Cys Leu Asp Gly Cys Lys Ser Glu Ala Xaa Lys Phe Thr Val Arg 50 gag gcc ctc aaa gaa aac caa gtt tcc ctc act gta aac aga gtg act Glu Ala Leu Lys Glu Asn Gln Val Ser Leu Thr Val Asn Arg Val Thr 65 70 cca aat gac agt gca att tac atc tgt gga ata gca ttc ccc agt gtg Ser Asn Asp Ser Ala Ile Tyr Ile Cys Gly Ile Ala Phe Pro Ser Val 80 85 ccg gaa gcg aga gct aaa cag aca gga gga ggg ggg acc aca ctg gtg gta Pro Glu Ala Arg Ala Lys Gln Thr Gly Gly Gly Thr Thr Leu Val Val 100 105 110 aga gaa att aag ctg ctc agc aag gaa ctg cgg agc ttc ctg aca gct Arg Glu Ile Lys Leu Leu Ser Lys Glu Leu Arg Ser Phe Leu Thr Ala 115 ctt gta tca ctg ctc tct gtc tat gtg acc ggt gtg tgc gtg gcc ttc 130 Leu Val Ser Leu Leu Ser Val Tyr Val Thr Gly Val Cys Val Ala Phe 130 135 135 140 ata ctc ctc tcc aaa tca aaa tcc aac cct cta aga aac aaa gaa ata 145 145 150 165 170 170 175 att gct caa gaa cta tac cat aag agg acd acg agg cat ttt cag gaa 626 674
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cagctccctg cctagcatcc atg acc tgt tgg atg tta cct cca atc agt ttc Met Thr Cys Trp Met Leu Pro Pro Ile Ser Phe -20 -15	
ctg tcc tac ctg cct ctt tgg ctt gga cct ata tgg cca tgc tct ggc Leu Ser Tyr Leu Pro Leu Trp Leu Gly Pro Ile Trp Pro Cys Ser Gly -10 -5	281
tct acc ctt ggg aag cct gat ccc ggt gtg tgg ccc agc ttg ttc agg Ser Thr Leu Gly Lys Pro Asp Pro Gly Val Trp Pro Ser Leu Phe Arg 5 10 15	329
ccc tgg gat gct gca tct cca ggc aac tat gca ctt tcc cgg gga rar Pro Trp Asp Ala Ala Ser Pro Gly Asn Tyr Ala Leu Ser Arg Gly Xaa 20 25 30 35	377
aac cak tat gav aak tgg ggg cag ggc aca cat tca tct ttg Asn Xaa Tyr Xaa Xaa Trp Gly Gln Gly Thr His Ser Ser Leu 40 45	419
targaaggte tggcetgggg terggtgaag gagggeeeag gteagttetg gggteeeagt gacetgettt geeattetee tggtgeeget getgeteeet gtttetggag etggatgtte eeeacetgge agttgagetg eetgageeaa tgtgtetgte tttggtaaet gagtgaaeea taataaaggg gaacatttgg eeetgtgaaa aaaaaaaa	479 539 599 637

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                                                                     215
Thr Ser Ser His Ala Ser Ser Leu His Leu Pro Pro Ser Cys Thr Arg
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Leu Thr Leu Thr Gln Thr Leu Arg Thr Gly Met His Leu Ser Arg Ala
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                                                                     312
Leu Gln Gly Thr Leu Thr Arg Leu Gln Ser Thr Pro Ala
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                                                                     372
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se	q VL	LLRQ	LFAQ	AEK/V	1Y										
	•														
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ctcccgtt	cc t	ttag	gctg	c cg	ccgc	tgcc	tgc	egee	atg	yca NI-	gay	Tou	995	. Len	
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												-90			1.00
aat gag	cac	cat	caa	aat	gaa	gtt	att	aat	tat	atg	cgt	ttt	gct	cgt	163
Asn Glu	His	His	Gln	Asn	Glu	Val	Ile	Asn	Tyr	Met	Arg	Phe	Ala	Arg	
ASH OIG	-85	****				-80			-		-75				
tca aag	-05			202			act	ata	gat	tcc	tac	ttc	caa	gac	211
Ser Lys	aga	gge	LLG	aya	T	T	Thr	yal .	yen	Ser	Cvs	Phe	Gln	Asp	
	Arg	GIA	Leu	Arg	Leu	ъÃг	1111	Val	ASP	-60	0,2			•	
-70					-65							~ ~ +	~~~	atc	259
ctc aag	gag	agc	agg	ctg	gtg	gag	gac	acc	-1	acc	ala ~1.	gat	922	1723	
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Ser Glu	7721	Len	Acn	Glv	Leu	Gln	Āla	Val	Val	His	Ser	Glu	Val	Glu	
Ser Gru	vai	пеп		GIY	шсы	02		-30					-25		
			-35						ata	++=	ctt	cta	cga	caq	355
tct gag	ctc	atc	aac	act	gcc	tat	acc	aat	yry	Tan	Ton	Len	Dya	Gln	
Ser Glu	Leu	Ile	Asn	Thr	Ala	Tyr	Thr	Asn	vaı	ьеи	Den	Deu	Arg	GIII	
		-20					-15					-10			403
ctg ttt	gca	caa	gct	gag	aag	tgg	tat	ctt	aag	cta	cag	aca	gac	acc	403
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	-5					1				5					
tct gaa	ctt	gaa	aac	cga	gaa	tta	tta	gaa	caa	ktt	gca	gaa	ttt	gaa	451
Ser Glu	TON	Glu	Acn	Ara	Glu	Leu	Leu	Glu	Gln	Xaa	Ala	Glu	Phe	Glu	
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10				15				224		atc	tta	dat	atc	aca	499
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Xaa Pro	LVE	Leu	Ala	Pro	Leu	Asn	Glu	Gly	Gly	Thr	Ala	Lys	Leu	Leu	
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aac aag	ats	. ata	tat	att	att	tta	aga	aac	qqa	aag	tct	ctc	att	ctg	595
Asn Lys	900	T 10	~~~	Tlo	Tle	Len	Aro	Asn	Glv	Lvs	Ser	Leu	Ile	Leu	
Asn Lys		1116	Cys	116	110	65	**** 5			-1-	70				
	60											. +++	att	tca	643
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Ser Cy	s Hi	s Cys	Leu	Gly	Trp	Arg	Asr	rrys	Ser	GIY	Arg	Pile	. vas	. Der	
75					80					85					c02
ggt cc	t ct	gago	ata	att	agt	cca	ttg	cag	, tag	itttt	act	tgat	ggta	acc	693
Gly Pr	o Lei	ı Arc	ılle	: Ile	Ser	Pro	Let	ı Glr	1						
90				95											
20		G 2.22	12000	,ca +	actt	aacc	t to	taga	agago	cto	aaqt	agc	tcct	gatcac	753
ccatgg	youa.	yaas	14995	,		.aucc		-+++	ישרטי	י מכנ	ittt:	itta	ato	gacattt	813
accttt	ccaa	ggta	iaagt	.ga a	yayo	.acyd	.a al		-++	, 4++	-+=+=	1222	atta	atttatc	873
aaagtt	tgtg	atct	gcgg	jta a	caag	igaga	ia y	guct		. gc			cto	atttatc	933
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agaatt	actt	gaag	ccqq	qqa g	gtgg	gaggt	t g	cagt	gagct	t gag	gatca	rcgc	Caci	tgcactc	1035
tagcct	gggc	gaca	agago	ga g	gacto	cato	t c	aaaa	aaaa	a aa					1032
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                                               -65
                                                                       100
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Ile Ser Ile Phe Pro Thr Met Met Val Cys Met Met Ala Trp Arg Pro
                     -55
                                         -50
att cag gca ctt atg gcc att tca gcc act ttc aag atg tta gaa agt
                                                                       148
Ile Gln Ala Leu Met Ala Ile Ser Ala Thr Phe Lys Met Leu Glu Ser
                -40
                                                                       196
tca ago cag aag tit ott cag ggt tig gio tat oto att ggg aac cig
Ser Ser Gln Lys Phe Leu Gln Gly Leu Val Tyr Leu Ile Gly Asn Leu
                                                     -15
                                 -20
            -25
                                                                       244
atg ggt ttg gca ttg gct gtt tac aag tgc cag tcc atg gga ctg tta
Met Gly Leu Ala Leu Ala Val Tyr Lys Cys Gln Ser Met Gly Leu Leu
                             -5
cct aca cat gca tcg gat tgg tta gcc ttc att gag ccc cct gag aga
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Pro Thr His Ala Ser Asp Trp Leu Ala Phe Ile Glu Pro Pro Glu Arg
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                                         15
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                                                                       340
Met Glu Ser Val Val Glu Asp Cys Phe Cys Glu His Glu Lys Ala Ala
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                                     30
cct ggt ccc tat gta ttt ggg tct tat tta cat cct tct tta agc cca
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 Pro Gly Pro Tyr Val Phe Gly Ser Tyr Leu His Pro Ser Leu Ser Pro
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                                 45
 gtg gct cct cag cat act ctt aaa cta atc act tat gtt aaa aaa aac
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 Val Ala Pro Gln His Thr Leu Lys Leu Ile Thr Tyr Val Lys Lys Asn
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 caa aaa act ctt ttc tcc atg gtg ggg tgacaggtcc taaaaggaca
 Gln Lys Thr Leu Phe Ser Met Val Gly
 atgtgcatat tacgacaaac acaaaaaaac tataccataa cccagggctg aaaataatgt
                                                                       603
 aaaaaacttt atttttgttt ccagtacaga gcaaaacaac aacaaaaaaa cataactatg
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ctctgtgcgc cacccctgag ttggatccag ggctagctgc tgttgacctc cccactccca
                                                                      240
egetgeeete etgeetgeag ee atg aeg eee etg ete aee etg ate etg gtg
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                         Met Thr Pro Leu Leu Thr Leu Ile Leu Val
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Val Leu Met Gly Leu Pro Leu Ala Gln Ala Leu Asp Cys His Val Cys
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gcc tac aac gga gac aac tgc ttc aac ccc atg cgc tgc ccg gct atg
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Ala Tyr Asn Gly Asp Asn Cys Phe Asn Pro Met Arg Cys Pro Ala Met
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                                15
gtt gcc tac tgc atg acc acg cgc acc tac tac acc ccc acc agg atg
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Val Ala Tyr Cys Met Thr Thr Arg Thr Tyr Tyr Thr Pro Thr Arg Met
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aag gtc agt aag tcc tgc gtg ccc cgc tgc ttc gar nac tgt gta
                                                                      481
Lys Val Ser Lys Ser Cys Val Pro Arg Cys Phe Glu Xaa Cys Val
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caccggcctt gccaccccgg ccaccctggc cctggcccc atcctcctgg ccaccctctg
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gggtctcctc taaagccccc gaggcagacc cactcaagaa caaagctctc gagacacact
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gctayaccct ckcacccakc tcaccctgcc tcaccctcca cactccctgc gacctcctca
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gccatgccca gggtcaggac tgtgggcaag aagacacccg acctccccca accaccacac
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WO 99/31236

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Pro Gln Trp Phe Val His Ser Ser Ala Leu Gly Leu Val Leu Ala Pro	
-15 -10 -5 1	
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Pro Phe Ser Ser Pro Gly Thr Asp Pro Thr Phe Pro Cys Ile Tyr Cys	•
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Cys Leu Cys Pro Asn Leu Lys Glu Val Cys Leu Ile Leu Pro Glu Lys	
35 40 45	
aat tgt aat agt cga cac gct gga ttt gta ggg cca sca aaa ttg cgg	296
Asn Cys Asn Ser Arg His Ala Gly Phe Val Gly Pro Xaa Lys Leu Arg	
50 55 60 65	240
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Gln	409
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aaaaaa	775

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gacagagatt ctcatga atg tgt cct gtg ttc tca aag cag ctg cta gcc	230
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-20 -15	
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Cys Gly Ser Leu Leu Pro Gly Leu Trp Gln His Leu Thr Ala Asn His

tgg cct cca ttc tcc sct ttc ctc tgt aca gtt tgc tct ggt tcc tca Trp Pro Pro Phe Ser Xaa Phe Leu Cys Thr Val Cys Ser Gly Ser Ser 10 15 20	326
gag cag att tcc gag tat act gct tca gcc acg ccc cca ctg tgc cgt Glu Gln Ile Ser Glu Tyr Thr Ala Ser Ala Thr Pro Pro Leu Cys Arg 25 30 35	374
tcc ctg aac caa gag cca ttc gty tca aga gcc att cgt cca aag tac Ser Leu Asn Gln Glu Pro Phe Val Ser Arg Ala Ile Arg Pro Lys Tyr 40 45 50	422
tot atc acc tagecattgt akccatacca ageogggett cetaettece Ser Ile Thr 55	471
totgotocco ttggtttcct cotgtraart aaatotoact gaccottgat goasotocaa goatatataa tatatatat ataaaaccat abtotaaaaa attoaaacca ggawaaataa	531 591
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ttc atc ggc att gga gaa att tta ggt gga agc ctc ttc ggc ctg ctg Phe Ile Gly Ile Gly Glu Ile Leu Gly Gly Ser Leu Phe Gly Leu Leu 20 25 30	194
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His Trp Gln Leu Leu Val Met Val Ile Phe Gly Phe Xaa Gly Thr Ile 150 155 160	
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Ser Phe Phe Thr Val Glu Trp Glu Xaa Ala Ala Phe Val Xaa Arg Gly	
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Met Ser Thr Trp Tyr Leu Ala Leu -80 -75	
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Asn Lys Ser Tyr Lys Asn Lys Asp Ser Val Arg Ile Tyr Leu Ser Leu	102
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-45

258

306

-50

-35

-55

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ttt aat tgg ttc gac tgc ctt ctc cac aat ttg ggc gag aat ttc ctt Phe Asn Trp Phe Asp Cys Leu Leu His Asn Leu Gly Glu Asn Phe Leu -25	-45 ttc att gcg agc ttg aaa gtt ctt ttc tat tac agt ttt agc ttt agg Phe Ile Ala Ser Leu Lys Val Leu Phe Tyr Tyr Ser Phe Ser Phe Arg	102
age ctt ctc age aaa agt tgt tct geg gac ceg tct ggg tca act ttc Ser Leu Leu Ser Lys Ser Cys Ser Ala Asp Pro Ser Gly Ser Thr Phe -5 1 5 atg agg gac att gag aca aac aaa tgaaatatgg gttaaagtac tctgagcagc Met Arg Asp Ile Glu Thr Asn Lys 10 15 tacaaaaaga araccagtct atcctgctgg agacagtggc cacgtgaara aagagctctt gcagtatgaa agaccacatg gaaagagagg ccacatggaa ccaacagtca gcatcttggt ttcggacacg tgaaraaatt catctcarac tgtgtatcct aaatcaggca cttgctgaat ctaactacat gagtgagacc agttgacaac acatggagca racatgagct gttctcagtg 492	ttt aat tgg ttc gac tgc ctt ctc cac aat ttg ggc gag aat ttc ctt Phe Asn Trp Phe Asp Cys Leu Leu His Asn Leu Gly Glu Asn Phe Leu	150
Met Arg Asp Ile Glu Thr Asn Lys 10 15 tacaaaaaga araccagtct atcctgctgg agacagtggc cacgtgaara aagagctctt gcagtatgaa agaccacatg gaaagagagg ccacatggaa ccaacagtca gcatcttggt ttcggacacg tgaaraaatt catctcarac tgtgtatcct aaatcaggca cttgctgaat ctaactacat gagtgagacc agttgacaac acatggagca racatgagct gttctcagtg 492	ago ott oto ago aaa agt tgt tot gog gao oog tot ggg toa act tto Ser Leu Leu Ser Lys Ser Cys Ser Ala Asp Pro Ser Gly Ser Thr Phe	198
tacaaaaaga araccagtct atcctgctgg agacagtggc cacgtgaara aagagctctt gcagtatgaa agaccacatg gaaagagagg ccacatggaa ccaacagtca gcatcttggt ttcggacacg tgaaraaatt catctcarac tgtgtatcct aaatcaggca cttgctgaat ctaactacat gagtgagacc agttgacaac acatggagca racatgagct gttctcagtg 492	Met Arg Asp Ile Glu Thr Asn Lys	252
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                                                                       117
ccc gag gct gtg gaa caa tca gcc cat ctc ttt gtg acc tgg agc agt
                                                                       165
Pro Glu Ala Val Glu Gln Ser Ala His Leu Phe Val Thr Trp Ser Ser
    -20
                         -15
                                             -10
                                                                      213
cag agg gcc ctc agt cac ccc gcc cca ttc ctc acc ara raa aar aat
Gln Arg Ala Leu Ser His Pro Ala Pro Phe Leu Thr Xaa Xaa Lys Asn
                    1
                                    5
                                                                       261
cca ttt cta tgg aag ctc tgacgtaact tcagtgtttt ctacaatact
Pro Phe Leu Trp Lys Leu
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cctcctgccc cgccccatta aaacagttct tttgttaaaa aatavcctaa tggtccaact
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ageettagtt teecatggee etgaaacaca cacattteee cetteette eeagaageea	180
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Met Ala	
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Phe Gln Ser Leu Leu Glu Met Lys Phe Phe Leu Cys Ala Ala Phe Pro	
-20 -15 -10 ctt gga gca gga gtg aag atg ttt cat tat ctt ggg cct ggg aaa cca	333
Leu Gly Ala Gly Val Lys Met Phe His Tyr Leu Gly Pro Gly Lys Pro	
-5 1 5 10	
ctt cyy cag get tet eee tee eee eae eee cat agg ame agg att tgg	381
Leu Xaa Gln Ala Ser Pro Ser Pro His Pro His Arg Xaa Arg Ile Trp	
15 20 25	
cct tagcttctgg gcctatcsgc tgccttccct cttyttccta ccacctcttc	434
Pro	
tgccttcctt trawctctgt tgggcttggg gatcttagtt ttcttttgtt tatttcccat	494
ctcatttttt tcttctggtc agttttttta agggggggtg ttgtggtttt ttgtttttgt	554
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ancideduced coducector dangement and amplement and	
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agagcaagtg gaatctctaa ga atg gct tcc agc cac tgg aat gaa acc act	172
Met Ala Ser Ser His Trp Asn Glu Thr Thr	
-45 -40	220
acc tet gtt tat cag tac ett ggt ttt caa gtt caa aaa att tac eet	220
Thr Ser Val Tyr Gln Tyr Leu Gly Phe Gln Val Gln Lys Ile Tyr Pro	
-35 -30 -25	260
tte cat gae aac tgg aac act gee tge ttt gte ate etg ett tta ttt	268
Phe His Asp Asn Trp Asn Thr Ala Cys Phe Val Ile Leu Leu Phe	
-20 -15 -10	316
ata ttt aca gtg gta tct tta gtg gtg ctg gct ttc ctt tat gaa gtg	210
Ile Phe Thr Val Val Ser Leu Val Val Leu Ala Phe Leu Tyr Glu Val	
-5 1 10 ctt gam wgc tgc tgc tgt gta aaa aac aaa acc gtg aaa gac ttg aaa	
	361
Leu Xaa Xaa Cys Cys Cys Val Lys Asn Lys Thr Val Lys Asp Leu Lys	364

WO 99/31236 -197agt gaa ccc aac cct ctt ara akt atg atg gac aac atc aga aaa cgt Ser Glu Pro Asn Pro Leu Xaa Xaa Met Met Asp Asn Ile Arg Lys Arg 30 35 40 gaa act gaa gtg gtc taacactcta taraaaatqa acaaaatctc tgaaagcagc 467 Glu Thr Glu Val Val 45 tcaacctctt ctgaraaaaa aaatatattc tgaggccaac tgttgctaca aaacaaattc 527 tgactgaatg gttaaaacat ttctagtara aggggaaaaa aaakttaaac atgcactgtt 587 tgtgtgtata sccatttcat taaatataca qtaaaactyc aaaaaaaaaa aa <210> 277 <211> 772 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 284..463

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Phe His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala
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Gly Val Ser Leu Pro Gly Ile Leu Ala Ala Lys Cys Gly Ala Glu Val
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Ile Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg
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Thr Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp
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Ile Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln
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His Thr Val Glu Met Leu Val Ile Ser Phe Ala Lys Asp Ser Leu
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                                   -105
tee eec cag gee etg gag gae teg gge eeg gtg aat ate tea gte tea
                                                                       101
Ser Pro Gln Ala Leu Glu Asp Ser Gly Pro Val Asn Ile Ser Val Ser
        -95
                             -90
                                                 -85
atc acc cta acc ctg gac cca ctg aaa ccc ttc.gga ggg tat tcc cgc
                                                                       149
Ile Thr Leu Thr Leu Asp Pro Leu Lys Pro Phe Gly Gly Tyr Ser Arg
                         -75
                                             -70
aac gtc acc cat ctg tac tca acc atc tta ggg cat cag att gga ctt
                                                                       197
Asn Val Thr His Leu Tyr Ser Thr Ile Leu Gly His Gln Ile Gly Leu
                    -60
                                         -55
tca ggc agg gaa gcc cac gag gag ata aac atc acc ttc acc ctg cct
                                                                      245
Ser Gly Arg Glu Ala His Glu Glu Ile Asn Ile Thr Phe Thr Leu Pro
                -45
                                     -40
aca gcg tgg agc tca gat gac tgc gcc ctc cac ggt cac tgt gag cag
                                                                      293
Thr Ala Trp Ser Ser Asp Asp Cys Ala Leu His Gly His Cys Glu Gln
                                 -25
gtg gta ttc aca gcc tgc atg acc ctc acg gcc agc cct ggg gtg ttc
                                                                      341
Val Val Phe Thr Ala Cys Met Thr Leu Thr Ala Ser Pro Gly Val Phe
        -15
                             -10
                                                 -5
ccg tca ctg tac agc cac cgc act gtg ttc ctg aca cgt aca gca acg
                                                                      389
Pro Ser Leu Tyr Ser His Arg Thr Val Phe Leu Thr Arg Thr Ala Thr
                                        10
cca cgc tct ggt aca aga tct tca caa ctg cca gag atg cca aca caa
                                                                      437
Pro Arg Ser Gly Thr Arg Ser Ser Gln Leu Pro Glu Met Pro Thr Gln
                                     25
aat acg ccc aaa att aca atc ctt tct ggt gtt ata agg ggg cca ttg
Asn Thr Pro Lys Ile Thr Ile Leu Ser Gly Val Ile Arg Gly Pro Leu
                                 40
gaa aag tot ato atg ott taaatoocaa gottacagtg attgttocag
                                                                      533
Glu Lys Ser Ile Met Leu
        50
atgatgaccg ttcattaata aatttgcatc tcatgcacac cagttacttc ctctttgtga
                                                                      593
tggtgataac aatgttttgc tatgctgtta tcaagggcag acctagcaaa ttgcgtcaga
                                                                      653
gcaatcctga attttgtccc gagaaggtgg ctttggctga agcctaattc cacagctcct
                                                                      713
tgttttttga gagagactga gagaaccata atccttgcct gctgaaccca gcctgggcct
                                                                      773
ggatgctctg tgaatacatt atcttgcgat gttgggttat tccagccaaa gacatttcaa
                                                                      833
gtgcctgtaa ctgatttgta catatttata aaaatctatt cagaaattgg tccaataatg
                                                                      893
cacgtgcttt gccctgggta cagccagagc ccttcaaccc caccttggac ttgaggacct
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1073

acctgatggg acgtttccac gtgtctctag agaaggatcc tggatctagc tggtcacgac

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ttcttgtttc agcccaatat gtagagaaca tttgaaacag tctgcacctt tgatacggta
                                                                   1133
ttgcatttcc aaagccacca atccattttg tggattttat gtgtctgtgg cttaataatc
                                                                   1193
ataqtaacaa caataatacc tttttctcca ttttqcttqc aqqaaacata ccttaaqttt
                                                                   1253
tttttgtttt gtttttgttt ttttgttttt tgttttcctt tatgaaqaaa aaataaaata
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                       -15
                                           -10
caa agg cca gag tca cag gaa gga ctt ctt cca ggg aga tta gtg gtg
                                                                     96
Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro Gly Arg Leu Val Val
atg gag agg aga gtt aaa aat gac ctc atg tcc ttc ttg tcc acg gtt
                                                                    144
Met Glu Arg Arg Val Lys Asn Asp Leu Met Ser Phe Leu Ser Thr Val
           15
                               20
ttg ttg agt ttt cac tct tct aat gca agg gtc tca cac tgt gaa cca
                                                                    192
Leu Leu Ser Phe His Ser Ser Asn Ala Arg Val Ser His Cys Glu Pro
                           35
ctt agg atg tgatcacttt caggtggcca ggaatgttga atgtctttgg
                                                                    241
Leu Arg Met
    45
ctcagttcat ttaaaaaaga tatctatttg aaagttctca rarttgtaca tatgtttcac
                                                                    301
agtacaggat ctgtacataa aagtttcttt cctaaaccat tcaccaagag ccaatatcta
                                                                    361
ggcattttct tggtagcaca aattttctta ttgcttaraa aattgtcctc cttgttattt
                                                                    421
ctgtttgtaa racttaagtg agttaggtct ttaaggaaag caacgctcct ctgaaatgct
                                                                    481
tgtctttttt ctgttgccga aatarctggt cctttttcgg gagttaratg tatarartgt
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ttgtatgtaa acatttcttg taggcatcac catgaacaaa gatatattt ctatttattt
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                                                                      104
Thr Ala Ala Ser Leu Arg Leu Glu Arg Asp Thr Arg Gln Leu Pro Leu
    -25
                        -20
ctc acc agt gcc ctg cac gga ctg cag cag cag cac cca gcc ttc tct
                                                                      152
Leu Thr Ser Ala Leu His Gly Leu Gln Gln Gln His Pro Ala Phe Ser
                    -5
                                        1
ggt gtg gca cgg ctg gcc aag cgg tgg gtg cgt gcc cag ctt ctt ggt
                                                                      200
Gly Val Ala Arg Leu Ala Lys Arg Trp Val Arg Ala Gln Leu Leu Gly
            10
                                15
gag ggt ttc gct gat gag agc ctg gat ctg gtg gcc gct gcc ctt ttc
                                                                      248
Glu Gly Phe Ala Asp Glu Ser Leu Asp Leu Val Ala Ala Ala Leu Phe
                            3.0
ctg cac cct gag ccc ttc acc cct ccg agt tcc ccc cag gtt ggc ttc
Leu His Pro Glu Pro Phe Thr Pro Pro Ser Ser Pro Gln Val Gly Phe
                        45
ctt cga ttc ctt ttc ttg gta tca acg ttt gat tgg aag aac aac ccc
                                                                      344
Leu Arg Phe Leu Phe Leu Val Ser Thr Phe Asp Trp Lys Asn Asn Pro
                   60
                                        65
ctc ttt gtc aac ctc aat aat gag ctc act gtg gag gag cag gtg gar
                                                                      392
Leu Phe Val Asn Leu Asn Asn Glu Leu Thr Val Glu Glu Gln Val Glu
                                    80
ate ege agt gge tte etg gea get egg gea eag ete eee gte atg gte
                                                                      440
Ile Arg Ser Gly Phe Leu Ala Ala Arg Ala Gln Leu Pro Val Met Val
            90
                                95
att gtt acc ccc caa rac cgc aaa aac tct gtg tgg aca cag gat gga
                                                                      488
Ile Val Thr Pro Gln Xaa Arg Lys Asn Ser Val Trp Thr Gln Asp Gly
                            110
ccc tca gcc car atc ctg cag cag ctt gtg gtc ctg gca gct gaa scc
Pro Ser Ala Gln Ile Leu Gln Gln Leu Val Val Leu Ala Ala Glu Xaa
                        125
ctg ccc atg tta rar aas cag ctc atg gat ccc cgg gga cct ggg gac
                                                                      584
Leu Pro Met Leu Xaa Xaa Gln Leu Met Asp Pro Arg Gly Pro Gly Asp
                    140
                                        145
atc agg aca gkg ttc cgg ccg ccc ttg gac att tac gac gtg ctg att
                                                                      632
Ile Arg Thr Xaa Phe Arg Pro Pro Leu Asp Ile Tyr Asp Val Leu Ile
                                    160
cgc ctg tct cct cgc cat atc ccg cgg cac cgc cag gct gtg gac tcr
                                                                      680
Arg Leu Ser Pro Arg His Ile Pro Arg His Arg Gln Ala Val Asp Ser
            170
                               175
cca gct gcc tcc ttc tgc cgg ggc ctg ctc agc cag ccg ggg ccc tca
                                                                      728
Pro Ala Ala Ser Phe Cys Arg Gly Leu Leu Ser Gln Pro Gly Pro Ser
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190

192 190 195	
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200 205 210 cag ctc arg gag gcc ttt ggg gat ctg gcc ctt ttc tat gac cag	024
Gln Leu Xaa Glu Ala Phe Gly Asp Leu Ala Leu Phe Phe Tyr Asp Gln	824
215 220 225 230	
cat ggt gga gag gtg att ggt gtc ctc tgg aag ccc acc agc ttc cag	872
His Gly Gly Glu Val Ile Gly Val Leu Trp Lys Pro Thr Ser Phe Gln 235 240 245	
ccg cag ccc ttc aag gcc tcc agc aca aag ggg cgc atg gtg atg tct	920
Pro Gln Pro Phe Lys Ala Ser Ser Thr Lys Gly Arg Met Val Met Ser	220
250 255 260	
cga ggt ggg gag cta gta atg gtg ccc aat gtt gaa gca atc ctg gag	968
Arg Gly Gly Glu Leu Val Met Val Pro Asn Val Glu Ala Ile Leu Glu	
265 270 275	
gac ttt gct gtg ctg ggt gaa ggc ctg gtg cag act gtg gag gcc cga	1016
Asp Phe Ala Val Leu Gly Glu Gly Leu Val Gln Thr Val Glu Ala Arg	
280 285 290	
agt gag agg tgg act gtg tgatcccagc tctggagcaa gctgtagacg	1064
Ser Glu Arg Trp Thr Val	
295 300	
gacagcagga cattggacct ctagagcaag atgtcagtag gatgacctcc accetecttg	1124
gacatgaatc ctccatggag ggcctgctgg ctgaacatgc tgaatcatct ccaacaaaac	1184
ccagccccaa ctttctctct gatgctccag cattggggca ggggcatggt ggcccatgta	1244
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Met Gly Gly Ile Trp Asn Ala Leu Ser Met Ser Ser Phe Ser	110
-15 -10	
ttt cat tca tcc tcc tgc tca gca ctg tca gcc aag agc tta ctc agc	350
Phe His Ser Ser Ser Cys Ser Ala Leu Ser Ala Lys Ser Leu Leu Ser	158
bor bor cys bor are bee ser are bys ser bee bee ser	

-5

206 .

-5 1 5 ₁₀	
aga cac cac ata ctg cag cag ttc cta gtg aga aga tct gtg cca cta	206
Arg His His Ile Leu Gln Gln Phe Leu Val Arg Lys Ser Val Pro Leu	200
15 20 25	
gaa aat gct tca ctt cca ttt cct cac ctg ggc agt tct ctg ttt aaa	254
Gid Ash Ala Ser Leu Pro Phe Pro His Leu Gly Ser Ser Leu Phe Lys	201
35 40	
att gtg ggc tgatttggtc ttcctctcct cctcccactg ttactgccct.	303
rie var Gry	303
45	
geagecettg tteaggtgta cagacectta ttetggeete tagtgteett gtetgteatg	363
acacaccci cogoccaaat acctotqaco ccaaqqotqq aatqqqqotq qtaqqarata	423
agreegetta decatareca tgecettet ettogeacet getteectge ggtgteetea	483
addysallic tgtgtggcag tggartgatt gcatgaattt ttctgtaaca cattaacttt	543
gracialla taagggartt tgaraaagct ttgcttataa tgtcaaggra aggaggtaaa	603
addrygaged daakaaatt deettaggge aagattatgt tataataraa aattgaattt	663
ceryaggeag tggctgccac coctiticar atgittagtc ctgcaaatag catciffett	723
grayrolding acategateg geatectage decettage deaggear tasactaget	783
caantigage collected aggaggetar aggaggetact eschartaat attraceact	843
aradayidal cittitaca aaacigitti totaqqtqqq tqqaaaqtqa aactqcaga	903
cooliging titageceaa rarateatti qeaacaacag tarateteeg gettteett	963
ctylettet attatgaaaa actatgttaa gggggaaaat gtggattatg gtaaccarag	1023
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	117
Met	
cca act ggc aag cag cta gct gac att ggc tat aag acc ttc tct acc	
Pro Thr Gly Lys Gln Leu Ala Asp Ile Gly Tyr Lys Thr Phe Ser Thr	165
tcc atg atg ctt ctc act gtg tat ggg ggg tac ctc tgg agt gtg age	0.00
Ser Met Met Leu Eur Thr Val Tyr Gly Gly Tyr Leu Cys Ser Val Arg	213
-5 -5 1	
gto tac cac tat tto cag tgg cgc agg gcc cag cgc cag gcc gca gaa	263
5 35 3-4 and age can ace aca dec	261

38.65

Val Tyr His Tyr Phe Gln Trp Arg Arg Ala Gln Arg Gln Ala Ala Glu 5 10	
	315
•	375
	435
	495
	536
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-15 -10	
	161
Thr Ala Ile Leu Ala Val Ala Val Gly Phe Pro Val Ser Gln Asp Gln	101
-5 1 5	
	209
Glu Arg Glu Lys Arg Ser Ile Ser Asp Ser Asp Glu Leu Ala Ser Gly	
10 15 20	
with the geg the cet tac cea tat cea tet ege cea ett cea cea att	257
Xaa Phe Val Phe Pro Tyr Pro Tyr Pro Phe Arg Pro Leu Pro Pro Ile	
25 30 35	
cca ttt cca aga ttt cca tgg ttt aga cgt aat ttt cct att cca ata	305
Pro Phe Pro Arg Phe Pro Trp Phe Arg Arg Asn Phe Pro Ile Pro Ile	
40 45 50 55	
cct gaa tct gcc cct aca act ccc ctt cct agc gaa aag taaacaaraa	354
cct gaa tct gcc cct aca act ccc ctt cct agc gaa aag taaacaaraa Pro Glu Ser Ala Pro Thr Thr Pro Leu Pro Ser Glu Lys	354
cct gaa tct gcc cct aca act ccc ctt cct agc gaa aag taaacaaraa Pro Glu Ser Ala Pro Thr Thr Pro Leu Pro Ser Glu Lys 60 65	
cct gaa tct gcc cct aca act ccc ctt cct agc gaa aag taaacaaraa Pro Glu Ser Ala Pro Thr Thr Pro Leu Pro Ser Glu Lys 60 65 ggaaaagtca crataaacct ggtcacctga aattgaaatt gagccacttc cttgaaraat	414
cct gaa tct gcc cct aca act ccc ctt cct agc gaa aag taaacaaraa Pro Glu Ser Ala Pro Thr Thr Pro Leu Pro Ser Glu Lys 60 65 ggaaaagtca crataaacct ggtcacctga aattgaaatt gagccacttc cttgaaraat caaaattcct gttaataaaa raaaaacaaa tgtaattgaa atagcacaca gcattctcta	

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 Lys Lys Val Leu Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val Gly
                                                                        107
                         -10
                                              -5
 ttc cca gtc tct caa gac cak gaa cga gaa aaa aga agt atc agt gac
                                                                       155
 Phe Pro Val Ser Gln Asp Xaa Glu Arg Glu Lys Arg Ser Ile Ser Asp
                                     10
 age gat gaa tta get tea ggg ttt ttt gtg tte eet tae eea tat eea
                                                                       203
 Ser Asp Glu Leu Ala Ser Gly Phe Phe Val Phe Pro Tyr Pro Tyr Pro
             20
                                 25
 ttt cgc cca ctt cca cca att cca ttt cca aga ttt cca tgg ttt aga
                                                                       251
 Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe Arg
         35
                             40
                                                 45
 cgt aat ttt cct att cca ata cct gaa tct gcc cct aca act ccc ctt
                                                                       299
Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro Thr Thr Pro Leu
                         55
                                             60
ccg agc gaa aag taaacaagaa ggaaaagtca cgataaacct ggtcacctga
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Pro Ser Glu Lys
65
aattgaaatt gagccactte ettgargaat caaaatteet gttaataaaa gaaaaacaaa
tgtaattgaa atagcacaca gcatteteta gtcaatatet ttagtgatet tetttaataa
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acatgaaagc aaaaaaaaa aa
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Met Thr Cys Arg Gly Ser	
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tgc agc tac gct acc agg aga tct cca agc gaa ctc agc ctc ctc cca	161
Cys Ser Tyr Ala Thr Arg Arg Ser Pro Ser Glu Leu Ser Leu Leu Pro	
-20 -15 -10	
age tee etg tgg gte eta gee aca age tet eca aca att act att gea	209
Ser Ser Leu Trp Val Leu Ala Thr Ser Ser Pro Thr Ile Thr Ile Ala	
-5 1 5	
	257
ctc gcg atg gcc gcc ggg aat ctg tgc ccc ctt cca tca tca tkt cgt	23,
Leu Ala Met Ala Ala Gly Asn Leu Cys Pro Leu Pro Ser Ser Xaa Arg	
10 15 20 25	
crc aaa agg cgc tgg tgt cag gca asc car caa ara gct ctg ctg	302
Xaa Lys Arg Arg Trp Cys Gln Ala Xaa Gln Gln Xaa Ala Leu Leu	
30 35 40	
tagetgecae tgaaaaraag geggtgaete eageteetee eataaagagg tgggagetgt	362
ceteggacca geettacetg tgacactgca cecteaegge caceegacta etttgeetee	422
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Met Val Pro Trp Pro	
- 55	
agg ggc aag gtg aaa act gct cct att ccc atc tct agg ttt cct ttc	223
Arg Gly Lys Val Lys Thr Ala Pro Ile Pro Ile Ser Arg Phe Pro Phe	
-50 -45 -40	
ctc cct acc cac gac cca ccc acc cca gca cat tgg tct cca gca tct	271
Leu Pro Thr His Asp Pro Pro Thr Pro Ala His Trp Ser Pro Ala Ser	
-35 -20	220
cat cag cag ttt aaa cat kkg tca ccc ctc ctc act ttg gcc ctg ctg	319
His Gln Gln Phe Lys His Xaa Ser Pro Leu Leu Thr Leu Ala Leu Leu	
-15 -10 -5	
-15	
ggt cag tgc tct ctg ttc arc aat ttg agg aaa aaa ctt gca ggg caa	367
ggt cag tgc tct ctg ttc arc aat ttg agg aaa aaa ctt gca ggg caa	367
	367
ggt cag tgc tct ctg ttc arc aat ttg agg aaa aaa ctt gca ggg caa Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys Lys Leu Ala Gly Gln	367 415

Lys A	la Lys 5	Lys	Leu	Pro	Ser 20	Phe	Ser	Ser	Leu	Pro 25	Leu	Thr	Leu	Trp	-
cca tt Pro Le 30	ta act eu Thr	cct Pro	caa Gln	ttt Phe 35	gct Ala	gag Glu	ctc Leu	act Thr	aca Thr 40	gtg Val	gca Ala	caa Gln	aaa Lys	aaa Lys 45	463
ttg ag Leu Ar	gg tgg rg Trp	tcc Ser	999 Gly 50	acc Thr	cta Leu	ggt Gly	tgg Trp	ggt Gly 55	cca Pro	gtt Val	ccc Pro	Ser	tgg Trp 60	att	511
caa tt Gln Ph	tt ttt ne Phe	tta Leu 65	ggg Gly	tgaa	atgga	agg (gara	gttgg	39 ga	actg	aaaas			aara	566
tatggt ktggtg	ttatt a tcaac d ggctc a ccagg a	egett atgeo	ggaa tgta	a at a ta	aktt atco	gaad	c aca	agtac tttgt	aat gar	aara	atatt aaktt	tt g	gaggo	tggga atcact	686 746
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ccctca	tgca t ggat a	aagt	ctgg	a ag	cctc	agc	atg	gct	tgt	gag	act Thr	cat	ggt	gtc	180 233
Leu Va	c cct l Pro -20	Ala 1	His	Leu	Ser	Gly -15	Leu	Ile	Thr	Cys	ctt Leu -10	ctt Leu	Ala	Phe	281
Trp Va -5		Ala	Ser	Cys	Ile 1	Gln	Arg	Cys	Ser 5	Gly	Ser	Pro	Leu	cca Pro 10	329
Leu	attcct														382
tctcaa	ctta g	actt	gact	t cc	tcca	agga	gct	ttgg	cta	tact	ctct	cc c	wcga	cccc	442
accctg	gcat a	ctac	acar	a tc	actc	tggg	ctc	actt	qcc	tacc	taat	aa t	catc	tecce	502
tggctt	ctgt a ggtg c	ctaa	cacc	y ag	ygca aaac	agga cart	caa	tass	gga tat	attt ttat	ttgt	at to	aaca	gtgcc	562
aaa		-33			9		Cua	-uad	-gr	LLYL	ccad	cy a	aaad	aaadd	622 625

ووائمة فالمسائد مناب الأناس أنفائه والمنطقة فيتعاطيه فيتطاع والمناطقة والمنطقة والمن

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                                                                      120
ttttgttctc tgctatgctc aggacccaga tcaaaggagc tcagtaacta tttacaggcg
                                                                       180
tacatcatat gtggaggaca cttatgctgt g atg gcc cca cac aca gct tcc
                                                                      232
                                   Met Ala Pro His Thr Ala Ser
                                        -35
ttt ggg gtc tgt ccc ctg ctc tcc gtt acc cgc gtg gta gcc act gag
                                                                      280
Phe Gly Val Cys Pro Leu Leu Ser Val Thr Arg Val Val Ala Thr Glu
                -25
                                     -20
cac tgg ctc ttc ctg gct tca ctc tct ggc atc aaa act tat cag tcc
                                                                      328
His Trp Leu Phe Leu Ala Ser Leu Ser Gly Ile Lys Thr Tyr Gln Ser
            -10
                                -5
                                                    1
tac atc tca gtc ttt tgc aag gtg aca ctt atc tgattaccta attcacacra
                                                                      381
Tyr Ile Ser Val Phe Cys Lys Val Thr Leu Ile
aggtgttaat ggtggtaatg gcataktatt tattacccca ggggacccak aacggtggta
                                                                      441
tcaaaacata tcattcccca gtggtttaaa actctggtag ctttccargg aatccaaagt
                                                                      501
ggaatccagt ctccttagct gawttcacag ggccccgtct gcacaacttg gcttctgtcg
                                                                      561
getteectan ecetgaette ceaageetta gteateacce teteteecac ecagggetea
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gcacagtacc tggaacagtc aagccctcaa taaatgttta ctgagtgcat yaaaaaaaa
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aaa
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<221> sig_peptide
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<210> 292

<222> 75..128
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 seq KMLISVAMLGAXA/GV

tion of the Control o

<221> polyA_signal <222> 595..600 <221> polyA site <222> 618..627 <400> 292 aagtgagacc gegeggeaac agettgegge tgegqqqaqe teecqtqqqc qetecqetqq 60 ctgtgcaggc ggcc atg gat tcc ttg cgg aaa atg ctg atc tca gtc gca Met Asp Ser Leu Arg Lys Met Leu Ile Ser Val Ala -15 -10 atg ctg ggc gca rgg gct ggc gtg ggc tac gcg ctc ctc gtt atc gtg 158 Met Leu Gly Ala Xaa Ala Gly Val Gly Tyr Ala Leu Leu Val Ile Val -5 1 acc ccg gga gag cgg cgg aag cag gaa atg cta aag gag atg cca ctg 206 Thr Pro Gly Glu Arg Arg Lys Gln Glu Met Leu Lys Glu Met Pro Leu 15 20 254 Gln Asp Pro Arg Ser Arg Glu Glu Ala Ala Arg Thr Gln Gln Leu Leu. 30 ctg gcc act ctg cag gag gca gcg acc acg cag gag aac gtg gcc tgg Leu Ala Thr Leu Gln Glu Ala Ala Thr Thr Gln Glu Asn Val Ala Trp 50 agg aag aac tgg atg gtt ggc ggc gaa ggc ggc gcc acg gga kgt cac 350 Arg Lys Asn Trp Met Val Gly Gly Glu Gly Gly Ala Thr Gly Xaa His 65 cgt gag acc gga ctt gcc tcc gtg ggc gcc gga cct tgg ctt ggg cgc 398 Arg Glu Thr Gly Leu Ala Ser Val Gly Ala Gly Pro Trp Leu Gly Arg 80 85 . agg aat ccg agg cag ctt tct cct tcg tgg gcc can cgg aaa atc cgg Arg Asn Pro Arg Gln Leu Ser Pro Ser Trp Ala Xaa Arg Lys Ile Arg 95 100 amc gaa aat wcc atg cca gga ctc tcc ggg gtc ctg tgaactgccg 492 Xaa Glu Asn Xaa Met Pro Gly Leu Ser Gly Val Leu 115 tegggtgage acgtgteece caaaccetgg actgactget ttaaggteeg caaggeggge 552 cagggccgag acgcgagtcg gatgtggtga actgaaagaa ccaataaaat catgttcctc 612 cammcaaaaa aaaaah

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<222> 50..244

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<221> polyA_signal

<222> 777..782

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<222> 801..812

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Ala Asp Ser Thr Glu Lys Ser Ala Ser Ala Ala Gly Thr Arg Asn Leu -45 -40 -35	154
cct ttt cag ttc tgt ctc cgg cag gct ttg agg atg aag gct gcg ggc Pro Phe Gln Phe Cys Leu Arg Gln Ala Leu Arg Met Lys Ala Ala Gly -30 -25 -20 -15	202
att ctg acc ctc att ggc tgc ctg gtc aca ggc gtc gag tcc aaa atc Ile Leu Thr Leu Ile Gly Cys Leu Val Thr Gly Val Glu Ser Lys Ile -10 -5	250
tac act cgt tgc aaa ctg gca aaa ata ttc tcg agg gct ggc ctg gac Tyr Thr Arg Cys Lys Leu Ala Lys Ile Phe Ser Arg Ala Gly Leu Asp 5 10 15	298
aat cyg agg ggc ttc agc ctt gga aac tgg atc tgc atg gcg tat tat Asn Xaa Arg Gly Phe Ser Leu Gly Asn Trp Ile Cys Met Ala Tyr Tyr 20 25 30	346
gag agc ggc tac aac acc aca gcc car acg gtc ctg gat gac ggc agc Glu Ser Gly Tyr Asn Thr Thr Ala Gln Thr Val Leu Asp Asp Gly Ser 35 40 45 50	394
atc gac tay ggc atc ttc caa atc aac agc ttc gcg tgg tgc aga cgc Ile Asp Tyr Gly Ile Phe Gln Ile Asn Ser Phe Ala Trp Cys Arg Arg 55 60 65	442
gga aag ctg aag gag aac aac cac tgc cay gtc gcc tgc tca gcc ttg Gly Lys Leu Lys Glu Asn Asn His Cys His Val Ala Cys Ser Ala Leu 70 75 80	490
rtc act gat gac ctc aca gat gca att atc tgt gcc arg aaa att gtt Xaa Thr Asp Asp Leu Thr Asp Ala Ile Ile Cys Ala Xaa Lys Ile Val 85 90 95	538
aaa gag aca caa gga atg aac tat tgg caa ggc tgg aag aaa cay tgt Lys Glu Thr Gln Gly Met Asn Tyr Trp Gln Gly Trp Lys Lys His Cys 100 105	586
gag ggg aga gac ctg tcc gas tgg aaa aaa ggc tgt gag gtt tcc Glu Gly Arg Asp Leu Ser Xaa Trp Lys Lys Gly Cys Glu Val Ser 115 120 125	631
taaactggaa ctggacccag gatgctttgc ascaacgccc tagggtttgc agtgaatgtc	691
caaatgcctg tgtcatcttg tcccgtttcc tcccaatatt ccttctcaaa cttggagagg	751
gaaaattaag ctatactttt aagaaaataa atatttccat ttaaatgtca amaaaaaaaaa ah	811 813

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<222> 154..576

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<222> 154..360

<223> Von Heijne matrix score 4.80000019073486 seq MMVLSLGIILASA/SF

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                                                                       120
ctggaaccaa cgggcacagt tggcaacacc atc atg aca tca caa cct gtt ccc
                                                                       174
                                      Met Thr Ser Gln Pro Val Pro
                                                      -65
aat gag acc atc ata gtg ctc cca tca'aat gtc atc aac ttc tcc caa
                                                                      222
Asn Glu Thr Ile Ile Val Leu Pro Ser Asn Val Ile Asn Phe Ser Gln
                             -55
gca gag aaa ccc gaa ccc acc aac cag ggg cag gat agc ctg aag aaa
                                                                      270
Ala Glu Lys Pro Glu Pro Thr Asn Gln Gly Gln Asp Ser Leu Lys Lys
                        -40
                                             -35
cat cta cac gca gaa atc aaa gtt att ggg act atc cag atc ttg tgt
                                                                      318
His Leu His Ala Glu Ile Lys Val Ile Gly Thr Ile Gln Ile Leu Cys
                    -25
                                         -20
ggc atg atg gta ttg agc ttg ggg atc att ttg gca tct gct tcc ttc
                                                                      366
Gly Met Met Val Leu Ser Leu Gly Ile Ile Leu Ala Ser Ala Ser Phe
                -10
                                    -5
tet eca aat tit ace caa gig act tet aca etg tig aac tet get tae
                                                                      414
Ser Pro Asn Phe Thr Gln Val Thr Ser Thr Leu Leu Asn Ser Ala Tyr
                            10
cca ttc ata gga ccc ttt ttt gtr akt aaa btt tct gag gag ggc agg
                                                                      462
Pro Phe Ile Gly Pro Phe Phe Val Xaa Lys Xaa Ser Glu Glu Gly Arg
                        25
                                            30
atg ggg caa ara ggg gag gaa rat vcc aat agc tta aac ttc cca sct
                                                                      510
Met Gly Gln Xaa Gly Glu Glu Xaa Xaa Asn Ser Leu Asn Phe Pro Xaa
                    40
                                        45
gcc agc ttg cta tkt ttg atc tgc cag gav caa gga ttc aac ggt gaa
                                                                      558
Ala Ser Leu Leu Xaa Leu Ile Cys Gln Xaa Gln Gly Phe Asn Gly Glu
                                    60
tot tgt tot cot gto ggg targataaca ggggttgott rattttagat
                                                                      606
Ser Cys Ser Pro Val Gly
            70
caatttctta tcagactcaa ataaacattt cttttgaaaa tcatcttatt cttcacatta
                                                                      666
tcatcttgag ctatgatgga aactagtgas ktctctccag gtttaggcga aaaaaaaatc
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seq MMVLSLGIILASA/SF

<221> polyA_signal

<222> 1017..1022

¥5.

<221> polyA_site <222> 1044..1054

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	> 29						raact	. ast	aset	++~	202	anto	מ בבי	nataa	agtaga	60
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ctac	aacc	aa c	aaac	acac	it to	qcaa	cacc	ato	ato	aca	a tca	caa	cct	gtt	ccc	174
	,		,,,,,	-		, ,									Pro	
													-65	;		
			atc													222
Asn	Glu		Ile	Ile	Val	Leu		Ser	Asn	Val	Ile		Phe	Ser	Gln	
		-60					-55					-50		-		270
			ccc Pro													270
Ald	-45	тур	PIO	GIU	PIO	-40	VOII	GIII	GIY	GIII	-35	Jer	шса	DyS	275	
cat		cac	gca	gar	rtc		att	att	aaa	act		caq	atc	ttq	tqt	318
His	Leu	His	Ala	Glu	Xaa	Lys	Val	Ile	Gly	Thr	Ile	Gln	Ile	Leu	Cys	
-30					-25	•			•	-20					-15	
			gta													366
Gly	Met	Met	Val	Leu	Ser	Leu	Gly	Ile	Ile	Leu	Ala	Ser	Ala	Ser	Phe	
				-10					- 5					1		
			ttt													414
Ser	Pro		Phe	Thr	GIN	vaı	Inr 10	ser	Thr	Leu	Leu	Asn 15	ser	Ala	Tyr	
CCa	ttc	5 ata	gga	ccc	` +++	+++		atc	atc	tct	aac		cta	tca	atc	462
			Gly													
	20		1			25					30					
gcc	aca	aaa	aaa	agg	tta	acc	aac	ctt	ttg	gtg	cat	acc	acc	ctg	gtt	510
Āla	Thr	Lys	Lys	Arg	Leu	Thr	Asn	Leu	Leu	Val	His	Thr	Thr	Leu	Val	
35					40					45					50	
			ctg													558
GIA	Ser	11e	Leu		Ala	Leu	Ser	Ата	Pen	vaı	GIY	Pne	116	лаа 65	Leu	
t ct	atc		cag	55	200	tta	aat	cct		tca	cta	cak	tat		tta	606
			Gln													• • • •
		•	70					75					80			
			aat													654
Xaa	Lys	Asn	Asn	Ile	Pro	Thr	Xaa	Xaa	Tyr	Val	Xaa	Tyr	Phe	Tyr	His	
		85					90					95	- \			500
			tat													702
Asp	100	ьeu	Tyr	Inr	Thr	105	лаа	Tyr	Inr	Ara	шув 110	Ald	Add	Leu	Ara	
gga		ctc	tct	cta	ato		att	tac	act	cta		gaa	ttc	tac	cwa	750
			Ser													
115					120			•		125				-	130	
sct	gtg	ctc	act	gct	gtg	ctg	cgg	tgg	aaa	cag	gct	tac	tct	gac	ttc	798
Xaa	Val	Leu	Thr	Ala	Val	Leu	Arg	Trp		Gln	Ala	Tyr	Ser			
				135					140					145		246
			gta													846
Pŗo	Gly	ser		Leu	Pne	Leu	Pro	155	ser	ıyr	11e	GIA	160	ser	Gly	
ato	tee	tca	150 aaa	ato	201	cat	asc		gga	tat	даа	gaa		tta	act	894
			Lys													-
		165	-				170	- 4 -	1	- 2 -		175				
tct	taa		aaa 🤄	ggga	gaaa	ta t	taat	caga	a ag	ttga	ttct	tate	gata	ata		947
Ser																
															tttaaa	1007
gta	atga	aca	ttaa	aaaa	aa c	catt	attt	c act	tgtc	aaaa	aaa	aaaaı	mCC 1	nKt		1060

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<222> 395..400
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gtgtcggacc tctagagcta atctcactag atgtgagcca ttgtttatat tctagccatc
                                                                  172
ctttcatttc attctagaag acccc atg caa gtt ccc cac cta agg gtc tgg
                          Met Gln Val Pro His Leu Arg Val Trp
                                                  -30
                               -35
                                                                  220
aca cag gtg awa gat acc ttc att ggt tat aga aat ttg gga ttt aca
Thr Gln Val Xaa Asp Thr Phe Ile Gly Tyr Arg. Asn Leu Gly Phe Thr
        -25
                           -20
agt atg tgc ata ttg ttc cac tgt ctt ctt agc ttt cag gtt ttc aaa
                                                                  268
Ser Met Cys Ile Leu Phe His Cys Leu Leu Ser Phe Gln Val Phe Lys
                       -5
aag aaa aga aaa ctt ara ctt ttc tgatgttctt ttttacgtaa ataaccattt
                                                                  322
Lys Lys Arg Lys Leu Xaa Leu Phe
               10
                                                                  382
tattgttgtt ttgctttttc tgccttcaaa ctactcccac aggccaaata tavctggctg
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444
<210> 297
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<222> 126..383

<221> sig peptide

<222> 126..167

<223> Von Heijne matrix score 7.5 seq VALNLILVPCCAA/WC

<221> polyA_signal

<222> 726..731

<221> polyA_site

<222> 743..754

<400> 297

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-10		170
tgt gac cca cgg agg atc cac tcc cag gat gac gtg ctc cgt agc tct Cys Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Leu Arg Ser Ser gct gct gat act ggg tct gcg atg cag cgg cgg gag gcc tgg gct Ala Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly 20 25 30 tgg aga agg tca caa ccc ttc tct gtt ggt ctg cct tct gct gaa aga Trp Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg 35 40 sct gag aac caa cca ggg aag ctg tcc tgg agg tcc ggg agg Leu Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu 55 60 65 gga cat aga atc tgt gac ctc tgacrrctgt gaasccacc tgggctacar 613 Gly His Arg Ile Cys Asp Leu 70 aaaaccacagt ctcccagca attattacaa ttcttgaatt ccttggggat tttttactgc cctttcaaag cacttaaktg tkrratctaa cgtkttccag tgtctgtctg aggtgactta aaaaatcaga acaaaacttc tattatccaa agtcatggga gagtacaccc tttccaggaa aaaagaaact ttctgaatg cctacctggc ggtgtatacc aggcagtgt cagtttaaa aaagagaaac tttctgaatg cctacctggc ggtgtatacc aggcagtgtg ccagtttaaa aagatgaaaa agaataaaaa cttttgagga aaaaaaaaaa		
Cys Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Leu Arg Ser Ser 1 get gat act ggg tct gcg atg cag cgg cgt gag gcc tgg gct ggt 266 Ala Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly 20 25 30 tgg aga agg tca cas ccc ttc tct gtt ggt ctg cct tct gct gaa aga 314 Trp Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg 35 40 45 cc gag aac caa cca ggg aag ctg tcg ggg gag gag ctc ggg aga 36c ctg gag aac ctg tcg tcg gag gac ctg ggt gag act ctg gag acc cag gga aac ctg tcg tcg tgg gag tcc ctg gt ggs gag ctg gag cat aga atc tgt gac ctc tgacrrctgt gaasccaccc tgggctacar 413 Gly His Arg Ile Cys Asp Leu 70 aaaccacagt cttcccagca attattacaa ttcttgaatt ccttggggat tttttactgc cctttcaaag cacttaaktg tkrratctaa cgtkttccag tgtctgtctg aggtgatca 533 aaagtttttg ggaaacactg aatagaaatc ttcccagtaa ttataaattgt gtatttaaaa aaaaaaaaaa	· · · · · · · · · · · · · · · · · · ·	210
S		210
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Arg Tyr Phe Tyr Asn Arg Thr Ser Lys Arg Cys Glu Thr Phe Val Phe

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Glu Val Xaa Cys Val Ala Lys Tyr Lys Pro Pro Arg 70

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ageggeaaga tegeatetee eggete atg gge gae tat etg etg ege ggt tae
                                                                      173
                             Met Gly Asp Tyr Leu Leu Arg Gly Tyr
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Asp Lys Gln Arg Lys Ile Tyr Cys Val Ala Cys Gln Glu Leu Asp Ser
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                                    -10
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Ser Arg Pro Ala Pro Gln Pro Pro Val Pro Arg Pro Glu His Cys Glu
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Gly Ala Ala Gly Leu Lys Ala Ala Gln Gly Pro Pro Ala Pro Ala
    15
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                                            25
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Val Pro Pro Asn Thr Xaa Val Met Ala Cys Thr Gln Thr Ala Leu Leu
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Gln Lys Leu Thr Trp Ala Ser Ala Glu Leu Gly Ser Xaa Thr Ser Xaa
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Gly Lys Xaa Ala Ser Ser Cys Val Ala Leu Ser Ala His Val Arg Arg
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Gly Asn Xaa Xaa Xaa Xaa Leu Ser Lys Arg Asp	
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Arg Leu	30					35					40			
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gat ttg Asp Leu	aag gt Lys Va	l Pro	agg Arg	atg Met	gag Glu	gar Glu 115	aag Lys	gag Glu	gcc Ala	ctg Leu	gta Val 120	ccc Pro	mtc Xaa	545
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-10 cys Ash Leu His Cys Ser Trp Leu His Ser Ser Pro Arg Pro Asp	
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Leu Pro Thr Ala His His Thr Leu Gly Leu Pro Val Gly Lys His Ile
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687

adi amiliadiki ka badiki dalimbali adi masabi da mada ka ma

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Tyr Val Ser Tyr Leu Phe Ser Thr Asn Ser Pro Leu Ser Phe Arg Arg
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Ser Ser Thr Pro Cys Asp Ser Lys Phe Pro Thr Val Tyr Ser Ser Ala
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Pro Phe His Ala Pro Leu Pro Val Gln Asn Ser Leu Trp Gly His Pro
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ete cat ggt tgt tee tgg caa tge cac cat eee cag gga car aat ete
Leu His Gly Cys Ser Trp Gln Cys His His Pro Gln Gly Gln Asn Leu
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Gln Pro Ala Ser Leu Xaa Thr His Leu Ser Lys Pro Lys Arg His Phe
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Xaa Lys Lys Xaa Cys Gln Ala
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                                       -20
-30
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                -10
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Tyr Lys Leu Gln Glu Arg Ser Asp Leu Thr Val Lys Glu Lys Glu Glu
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                            10
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Leu Ile Glu Glu Trp Gln Pro Glu Pro Leu Val Pro Pro Val Pro Lys
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Asp His Pro Ala Leu Asn Tyr Asn Ile Val Ser Gly Pro Pro Ser His
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Ser Leu Lys Lys Tyr Gly Val Gly Thr Cys Gly Pro Cys Gly Phe Tyr
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Gly Thr Phe Glu
    100
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gtt gac cca cag ttc ctg aaa ctc acc aaa gta gat gac caa att tac Val Asp Pro Gln Phe Leu Lys Leu Thr Lys Val Asp Asp Gln Ile Tyr 30 35 40	ļ													
tct gag ttc cgg aaa aat ttt gag acc ctt agg ata gat gtg ttg grc 292 Ser Glu Phe Arg Lys Asn Phe Glu Thr Leu Arg Ile Asp Val Leu Xaa 45 50 55	?													
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A MARTER CONTROLLED CONTROL CO

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Leu Ser Ser Cys Leu Leu Pro Leu Cys Trp Leu Glu Arg Lys Asp His
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tot tat cag gag cag gag cta cag gat ttt ctt ctg tct cag atg tca	202												
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60 65 70													
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75 80 85 90													
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Cys Leu His Leu Ala Leu Val Tyr Tyr Asp Phe Phe Gln Met Phe Pro													
110 115 120													
aaa raa gtt too ara aac ttt gac ttg aaa tgt ttg car atc aac tat	634												
Lys Xaa Val Ser Xaa Asn Phe Asp Leu Lys Cys Leu Gln Ile Asn Tyr													
125 130 135	602												
aag cac aaa gaa gar ata act too aaa aga gtg ctg ttt tta aaa ata	682												
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<222> 672..752

المرابط والمرافع والمرافع والمستعد ومنافع والمستري والمناف ومماه بالمرافع والمرافع والمرافع والمرافع والمماعي والمعلى

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                                                                      710
             Met Val Val His Leu Leu Tyr Ala His Leu Ser Phe Thr
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                                                                      752
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Ser Lys Arg Ala Val Val Met Leu Lys Leu Glu Ile Thr Phe
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cag ggc ttc cat agc tct tta tgt gca ctt cga tcc cag cat ttt cca Gln Gly Phe His Ser Ser Leu Cys Ala Leu Arg Ser Gln His Phe Pro 30 35 40	251
tcg act tgt aat tgt ttc tgc tac ctg aca atc atc gcc ttg drd tac Ser Thr Cys Asn Cys Phe Cys Tyr Leu Thr Ile Ile Ala Leu Xaa Tyr 45 50 55	299
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cag ttt tct tac ctt tgc ctg ccc tgc ctt tca tgg aat aar aaa ggc Gln Phe Ser Tyr Leu Cys Leu Pro Cys Leu Ser Trp Asn Lys Lys Gly 15 20 25	208
aac gtt ttg cag ctt cca aat ttc tgaaraaact aatctcarat tggcagttaa Asn Val Leu Gln Leu Pro Asn Phe 30 35	262
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and the control of th

622

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		10			_	_	15					20				
														atc Ile		344
-	25					30					35					200
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40			*		45					50					55	
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хаа	GIN	GIN	Pro	Asn 60	GIY	Sei	Leu	ser	65	ASII	116	Sei	ser	Ser 70	urs	
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Ala	Pro	Хаа	Pro 75	Xaa	Thr	Cys	Thr	Leu 80	GIU	Pro	GIY	vaı	Asp 85	Pro	Thr	
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Arg	Xaa	90 90	Cys	lle	Asn	Pro	н1S	Pro	Pro	Pro	Pro	11e	ьeu	Lys	лаа	
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Pro	Leu 105	Ser	Pro	Tyr	Pro	Lys 110	Pro	Gln	Leu	Gly	Thr 115	His	Ala	Gly	Gin	
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Val 120	Asn															
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-70

-65

-60

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-55

-50

-45

ccg ctc att acc ttg cag tat ttt tct ctg gaa atc ctt gta atc ttg

1.59

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Lvs	Glu	Trp	Thr	Ser	Lys	Leu	Trp	His	Arg	Gln	Ser	Ile	Val	Val	Ser	
/	-25				•	-20	-		_		-15					
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Phe	Leu	Leu	Leu	Leu	Ala	Gly	Leu	Ile	Ala	Thr	Tyr	Tyr	Val	Glu	Gly	
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Val	His	Gln	Gln	Tyr	Val	Gln	Arg	Ile	Glu	Lys	Gln	Phe	Leu	Leu	Tyr	
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Ala	Tyr	Trp	Ile	Gly	Leu	Gly	Ile	Leu	Ser	Ser	Val	Gly	Leu	Gly	Thr	
	_	25					30					35				
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Gly	Leu	His	Thr	Phe	Leu	Leu	Tyr	Leu	Gly	Pro	His	Ile	Ala	Ser	Val	
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Tyr	Pro	Asp	Gln	Ile	Ile	Cys	Pro	Asp	Glu	Glu	Gly	Thr	Glu	Gly	Thr	
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Ile	Ser	Leu	Trp	Ser	Ile	Ile	Ser	Lys	Val	Arg	Ile	Glu	Ala	Cys	Met	
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Trp	Gly	Ile	Gly	Thr	Ala	Ile	Gly	Glu	Leu	Pro	Pro		Phe	Met	Ala	
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gaa	ttt	gaa	gag	atg	ctg	gaa	cat	gca	gag	tct	gca	caa	gta	aga	aca	795
Glu	Phe	Glu	Glu	Met	Leu	Glu	His	Ala	Glu			Gln	Val	Arg	Thr	
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gtg	999	ata	gaa	aat	aga	aca	ctt	tac	tto	ttc	cta	aag	agg	cta	tta	843
Val	Gly	Ile	Glu			Thr	Leu	Туг			Leu	rys	Arg	Leu	Leu	
				155					160					165		901
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cccaagaaga ctgggga atg gag aga cag tca agg gtt atg tca gaa aag	170
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gat gag tat cag ttt caa cat cag gga gcg gtg gag ctg ctt gtc ttc	218
Asp Glu Tyr Gln Phe Gln His Gln Gly Ala Val Glu Leu Leu Val Phe	
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Asn Phe Leu Leu Ile Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn	
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His Arg Phe Arg Phe Leu His Glu Thr Gly Gly Ala Met Val Tyr Gly	
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Leu Xaa Met Gly Leu Ile Leu Xaa Tyr Ala Thr Ala Pro Thr Asp Ile	
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Glu Ser Gly Xaa Val Tyr Asp Cys Val Lys Leu Thr Phe Ser Pro Ser	
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Thr Leu Leu Val Asn Ile Thr Asp Gln Val Tyr Glu Tyr Lys	
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Leu Trp Lys Ile Ser Gly Cys Glu Glu Val Pro Leu Thr Tyr Asn Leu											
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Leu Lys Cys Leu Leu Asp Lys Ala His Cys Val Leu Leu Thr Pro Cys											
15 20 25	210										
ggt tac atc ttt tcc ttg atc agt cca gaa att ctc aaa ctc act tta	312										
Gly Tyr Ile Phe Ser Leu Ile Ser Pro Glu Ile Leu Lys Leu Thr Leu 30 35 40											
	360										
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45 50 55											
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60 65 70											
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Lys	101										
75 75											
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<221> polyA site

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<222> 112..450

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<222> 1095..1106

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Phe Leu Leu Glu Gly Gly Xaa Thr Glu Gln Val Xaa His Ser Glu

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aca tat tgc atg ttt caa gac aag aag tac aga gtg ggt gag aga tgg	261
Thr Tyr Cys Met Phe Gln Asp Lys Lys Tyr Arg Val Gly Glu Arg Trp 10 15 20	
cat cct tac ctg gaa cct tat ggg ttg gtt tac tgc gtg aac tgc atc	309
His Pro Tyr Leu Glu Pro Tyr Gly Leu Val Tyr Cys Val Asn Cys Ile 25 30 35	
tgc tca gag aat ggg aat gtg ctt tgc agc cga gtc aga tgt cca aat	357
Cys Ser Glu Asn Gly Asn Val Leu Cys Ser Arg Val Arg Cys Pro Asn	33,
40 45 50 55	
gtt cat tgc ctt tct cct gtg cat att cct cat ctg tgc tgc cct cgc	: 405
Val His Cys Leu Ser Pro Val His Ile Pro His Leu Cys Cys Pro Arg	. 105
60 65 70	
tgc cca gaa gac tcc tta ccc cca gtg aac aat rwg gtg acc agc	450
Cys Pro Glu Asp Ser Leu Pro Pro Val Asn Asn Xaa Val Thr Ser	
75 80 85	
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tggcacccaa acctccgggc atttggcatt gtggagtgtg tgctatgtac ttgtaatgtc	990
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Met	167
agg att ctg cag tta atc ctg ctt gct ctg gca aca ggg ctt gta ggg Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val Gly	101
-15 -10 -5	
gga gag acc agg atc atc aag ggg ttc gag tgc aag cct cac tcc cag	215
Gly Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Pro His Ser Gln	-10
1 5 10 15	

																262
	: tgg															263
Pro	Trp	Gln	Ala		Leu	Phe	Glu	Lys		Arg	Leu	Leu	Cys		Ala	
				20					25 -					30		
-	g ctc		_		-			_		_	_		_		_	311
Thi	Leu	Ile	Ala	Pro	Arg	Trp	Leu	Leu	Thr	Ala	Ala	His	Cys	Leu	Lys	
			35					40					45			
CCC	cgc	tac	ata	ktt	cac	ctg	999	cag	cac	aac	ctc	cag	aag	gag	gag	359
Pro	Arg	Tyr	Ile	Xaa	His	Leu	Gly	Gln	His	Asn	Leu	Gln	Lys	Glu	Glu	
		50					55					60				
ggd	tgt:	gag	car	acc	cgg	aca	gcc	act	gag	tcc	ttc	CCC	cac	CCC	ggc	407
Gly	Cys	Glu	Gln	Thr	Arg	Thr	Ala	Thr	Glu	Ser	Phe	Pro	His	Pro	Gly	
-	65					70					75					
tto	aac	aac	aqc	ctc	ccc	aac	aaa	qac	cam	mqc	aat	qac	atc	atg	ctg	455
	a Asn		_					_		_		_		_	_	
80					85		-	•		90		•			95	
	g aak	atσ	ama	tea	cca	atc	tcc	atc	acc	taa	act	ata	cga	ccc	ctc	503
	l Xaa															_
vu.			41UU	100		,,,			105		****		••••	110		
200	a ata	+	+		+~+	atc	201	act		200	200	tac	ctc		tcc	551
	c ctc c Leu															331
1111	ьец	ser		Arg	Cys	vai	1111	120	GIY	1111	261	Cys	125	116	361	
			115													599
	tgg		-	_		_		_		_	_				_	393
GT.	y Trp	•	ser	Thr	ser	ser		GIN	ьeu	Arg	ьeu		HIS	Thr	Leu	
		130					135					140				
_	a tgc	_								_	_	-				647
Arg	g Cys	Ala	Asn	Ile	Thr		Ile	Glu	His	Gln	•	Cys	Glu	Asn	Ala	
	145					150					155					
	ccc															695
Ту	r Pro	Gly	Asn	Ile	Thr	Asp	Thr	Met	Val	Cys-	Ala	Ser	Val	Gln		
16)				165					170					175	
999	g ggc	aag	gac	tcc	tgc	cag	ggt	gac	tcc	999	ggc	cct	ctg	gtc	tgt	743
Gl	, Gly	Lys	Asp	Ser	Cys	Gln	Gly	Asp	Ser	Glý	Gly	Pro	Leu	Val	Cys	
				180					185					190		
aa	c cag	tct	ctt	caa	ggc	att	atc	tcc	tgg	ggc	cag	gat	ccg	tgt	gcg	791
As	a Gln	Ser	Leu	Gln	Gly	Ile	Ile	Ser	Trp	Gly	Gln	Asp	Pro	Cys	Ala	
			195					200					205			
at	c acc	cga	aag	cct	ggt	gtc	tac	acg	aaa	gtc	tgc	aaa	tat	gtg	gac	839
	e Thr		_											_		
		210	-		-		215		-		-	220				
tq	g atc	caq	qaq	acq	atq	aaq	aac	aat	taga	actq	ac d	ccac	ccac	ca		886
	lle	_		_	_	_										
	225					230										
ca		tca	aceti	ccati	tt c		taata	a tti	taati	tact	atte	cacto	cta	ttaai	caagaa	946
	_										_		_		atgctg	1006
		-	_			_						-			gccttg	1066
						•				-					agcccc	1126
						-				-	_	-			aaaaaa	1186
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ua	~uc															

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cgg gaa att aaa aag caa ctg ctg ctt att gcg ggc ctt acc cgg gag Arg Glu Ile Lys Lys Gln Leu Leu Leu Ile Ala Gly Leu Thr Arg Glu 10 15 20	147
cgg ggc cta cta cac agt agc aaa tgg tcg gcg gag ttg gct ttc tct Arg Gly Leu Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser 25 30 35 40	195
ctc cct gca ttg cct ctg gcc gag ctg caa ccg cct ccg cct att aca Leu Pro Ala Leu Pro Leu Ala Glu Leu Gln Pro Pro Pro Pro Ile Thr 45 50 55	243
gag gaa gat gcc cag gat atg gat gcc tat acc ctg gcc aag gcc tac Glu Glu Asp Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr 60 65 70	291
ttt gac gtt aaa gag tat gat cgg gca gca cat ttc ctg cat ggc tgc Phe Asp Val Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys 75 80 85	339
aat gca aga aaa gcc tat ttt ctg tat atg tat tcc aga tat ctg gtg Asn Ala Arg Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val 90 95 100	387
agg gcc att tta aaa tgt cat tct gcc ttt agt gaa aca tcc ata ttt Arg Ala Ile Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe 105 110 115 120	435
aga acc aat gga aaa gtt aaa tct ttt aaa tagcttagca gtgggccact Arg Thr Asn Gly Lys Val Lys Ser Phe Lys 125 130	485
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tta Leu	ctc Leu	ggt Gly	ggt Gly	ggc Gly -5	gga Gly	gtc Val	tac Tyr	gga Gly	agc Ser 1	cgt Arg	Phe	cgc Arg	ttc Phe 5	act Thr	ttt Phe	97
cct Pro	ggc Gly	tgt Cys 10	aga Arģ	gcg Ala	ctt Leu	tcc Ser	ccc Pro 15	tgg Trp	cgg Arg	gtg Val	aga Arg	vtg Xaa 20	cag Gln	aga Arg	cga Arg	145
agg Arg	tgc Cys 25	gag	atg Met	agc Ser	act Thr	atg Met 30	ttc Phe	gcg Ala	gac Asp	act Thr	ctc Leu 35	ctc Leu	atc Ile	gtt Val	ttt Phe	193
atc Ile 40	tct	gtg Val	tgc Cys	acg Thr	gct Ala 45	ctg	ctc Leu	gca Ala	gag Glu	ggc Gly 50	ata	acc Thr	tgg Trp	gtc Val	ctg Leu 55	241
att	tac Tyr	agg Arg	aca Thr	gac Asp 60	aag	tac Tyr	aag Lys	aga Arg	ctg Leu 65	aag	gca Ala	gaa Glu	gtg Val	gaa Glu 70	aaa Lys	289
cag Gln	agt Ser	aaa Lys	aaa Lys 75	ttg	gaa Glu	aag Lys	aag Lys	aag Lys 80	gaa	aca Thr	ata Ile	aca Thr	gag Glu 85	tca Ser	gct Ala	337
ggt Gly	cga Arg	caa Gln 90	cag	aaa Lys	aar Lys	aaa Lys	ata Ile 95	gag	aga Arg	cdd Xaa	kaa Xaa	kas Xaa 100	amc Xaa	ctg Leu	arg Xaa	385
aat Asn	aac Asn 105	aac	aga Arg	gat Asp	cta Leu	tca Ser 110	atg	gtt Val	cga Arg	atg Met	aaa Lys 115	tcc Ser	atg Met	ttt Phe	gct Ala	433
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gat	ggt Gly	aga Arg	gtg Val	gtg Val 140	gca	aag Lys	ctt Leu	cct Pro	ttt Phe 145	acc	cct Pro	ctt Leu	tct Ser	tas Xaa 150	rtc Xaa	529
sra Xaa	gga Gly	ctg Leu	tct Ser 155	cat	cga Arg	aat Asn	ctg Leu	ctg Leu 160	gga	gat Asp	gac Asp	acc Thr	aca Thr 165	gac Asp	tgt Cys	577
tcc Ser	ttc Phe	att Ile 170	ttc	ctg Leu	taw Xaa	att Ile	ctc Leu 175	tgt	act Thr	atg Met	tcg Ser	att Ile 180	cga	cag Gln	aac Asn	625
att Ile	cag Gln 185	aaq	att Ile	ctc Leu	ggc Gly	ctt Leu 190	gcc	cct Pro	tca Ser	cga Arg	gcc Ala 195	gcc Ala	acc Thr	aag Lys	cag Gln	673
Ala	ggt	gga Gly	ttt Phe	ctt Leu	ggc Gly	cca Pro	cca Pro	cct Pro	cct Pro	tct Ser 210	999	aag Lys	ttc Phe	tct Ser		718
aac	tgtt	ttg	tasc	aaga	gc c	ttct atag	gtag	c ct	tack	taga actt	999	cctc	ttt	ctag	actggc ttttga tgatag	778 838 898

tgcttttggt cctagatgat ttttatcaaa taagtggatt gattagttaa gttcaggtaa tgtttatgta atgaaaaaca aatagcatcc ttcttgtttc atttacataa gtattttctgtgggaccgac tctcaaggca ctgtgtatgc cctgcaagtt ggctgtctat gagcatttag agatttagaa gaaaaattta gtttgtttaa cccttgtaac tgtttgtttt tttttcaag ccaaatacat gacataarat caataaarag gccaaatttt tasctgtttt atgtaaaaaa aaaaa	1018 1078 1138
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aca atc gca aaa tyc rrg gcs tva gag ggc ctc cga gac ccc tat ggc Thr Ile Ala Lys Xaa Xaa Ala Xaa Glu Gly Leu Arg Asp Pro Tyr Gly -80 -75 -70	160
cgc ctc tgt ggt agc gag cac ccc cga aga cca cct gag cgg ccc gag Arg Leu Cys Gly Ser Glu His Pro Arg Arg Pro Pro Glu Arg Pro Glu -65	208
gaa gac ccg agc act cca gag gag gcc tct acc acc cct gaa gaa gcc Glu Asp Pro Ser Thr Pro Glu Glu Ala Ser Thr Thr Pro Glu Glu Ala	256
	304
-50 -45 -40 tcg agc act gcc caa gca caa aag cct tca gtg ccc cgg agc aat ttt Ser Ser Thr Ala Gln Ala Gln Lys Pro Ser Val Pro Arg Ser Asn Phe	
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-50 -45 -40 tcg agc act gcc caa gca caa aag cct tca gtg ccc cgg agc aat ttt Ser Ser Thr Ala Gln Ala Gln Lys Pro Ser Val Pro Arg Ser Asn Phe -35 -30 -25 -20 cag ggc acc aag aaa agt ctc ctg atg tct ata tta gcg ctc atc ttc	352 400
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tcg agc act gcc caa gca caa aag cct tca gtg ccc cgg agc aat ttt Ser Ser Thr Ala Gln Ala Gln Lys Pro Ser Val Pro Arg Ser Asn Phe -35 -30 -25 -20 cag ggc acc aag aaa agt ctc ctg atg tct ata tta gcg ctc atc ttc Gln Gly Thr Lys Lys Ser Leu Leu Met Ser Ile Leu Ala Leu Ile Phe -15 -10 -5 atc atg ggc aac agc gcc aag gaa gct ctg gtc tgg aaa gtg ctg ggg Ile Met Gly Asn Ser Ala Lys Glu Ala Leu Val Trp Lys Val Leu Gly 1 5 10 aag tta gga atg cag cct gga cgt cas cac agc atc ttt gga gat ccg Lys Leu Gly Met Gln Pro Gly Arg Xaa His Ser Ile Phe Gly Asp Pro	400

ccc cga gca cac gtg gaa tcg agc ara ctg aaa stc wtg cat ttt gtg Pro Arg Ala His Val Glu Ser Ser Xaa Leu Lys Xaa Xaa His Phe Val 65 70 75	2
gca agg gtt cgt aac cga tgc tct aaa gac tgg cct tgt aat tat gac Ala Arg Val Arg Asn Arg Cys Ser Lys Asp Trp Pro Cys Asn Tyr Asp 80 85 90	0
tgg gat tcg gac gat gat gca gag gtt gag gct atc ctc aat tca ggt Trp Asp Ser Asp Asp Ala Glu Val Glu Ala Ile Leu Asn Ser Gly 95 100 105	8
gct arg ggt tat tcc gcc cct taagtaratc tgaggcagac ccttgggggt 739 Ala Xaa Gly Tyr Ser Ala Pro 110 115	9
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Met Asn Val Gly Thr Ala His Xaa Xaa Val Asn Pro Asn Thr Arg -35 -30 -25	
gtk atg aac age cgt ggc atc tgg ctc tcc tac gtg ctg gcc atc ggt 159	5
Val Met Asn Ser Arg Gly Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly -20 -15 -10	
ctc ctc cac atc gtg ctg ctg agc atc ccg ttt gtk agt gtc cct gtc 203 Leu Leu His Ile Val Leu Leu Ser Ile Pro Phe Val Ser Val Pro Val	3
-5 1 5	7
Val Trp Thr Leu Thr Asn Leu Ile His Asn Met Gly Met Tyr Ile Phe	1
10 15 20 ctg cac acg gtg aag ggg aca ccc ttt gag acc ccg gac cag ggc aag 299	9
Leu His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys 25 30 35 40	
gcg agg ctg cta acc cac tgg tgagcagatg gattatgggg tccagttcac 350	0
Ala Arg Leu Leu Thr His Trp 45	
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BO SETTING TO A STATE OF A

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530

590

650

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710
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Met Arg Thr Leu Phe Gly Ala Val Arg Ala Pro Phe Ser Ser Leu Thr
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Leu Leu Ile Thr Pro Ser Pro Ser Pro Leu Leu Phe Asp Arg Gly
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Leu Ser Leu Arg Ser Ala Met Ser
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gctatttaga tacaaactta aaacatacta tatattttaa ggatctaaga atcctttara
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WO 99/31236

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Gly Leu Arg Leu Phe Gly Ile Leu Ser Thr Cys Arg Val His His Thr
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atg aat cag ttc cta att gat ata tct agc ttt acc tcc cga gtt aaa
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Met Asn Gln Phe Leu Ile Asp Ile Ser Ser Phe Thr Ser Arg Val Lys
aaa aaa atc ttt tta ttt tat gcc ttc awa ggt tgc ycg ttt car agt
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Lys Lys Ile Phe Leu Phe Tyr Ala Phe Xaa Gly Cys Xaa Phe Gln Ser
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gcc aca taaataaaat gtttaacaaa aaaaaaaaa
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                                                                      158
Pro Leu Xaa Ala Glu Pro Thr Ala Glu Gly Glu Pro His Leu Pro Thr
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Ile 10	Thr	Tyr	Asn	Ile	His 15	Leu	Arg	Ala	ctc Leu	Phe 20	Tyr	Leu	Phe	Trp	Leu 25	338
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Met Gly Trp Gln Arg	290
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379

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Ser Trp Val Pro Xaa Ser Pro Asp Thr Gly Leu Xaa Pro Leu Thr Val	
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Arg Arg His Val Pro Ala Xaa Trp Val Leu Leu Xaa Arg Asp Pro Leu	
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345

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Met His Gly Leu Leu His Tyr Leu Phe His Thr Arg Asn -25 -20 cac acc ttc att gtc ctg cac ctg gtc ttg caa ggg atg gtt tat act His Thr Phe Ile Val Leu His Leu Val Leu Gln Gly Met Val Tyr Thr -15 -10 -5 gag tac acc ttg gaa gta ttt ggc tac tgt cag gag ctg gag ttg tcc Glu Tyr Thr Trp Glu Val Phe Gly Tyr Cys Gln Glu Leu Glu Leu Ser 1 15 ttg cat tac ctt ctt ctg ccc tat ctg ctg cta ggt gta aac ctg ttt Leu His Tyr Leu Leu Leu Pro Tyr Leu Leu Gly Val Asn Leu Phe 20 25 30 ttt ttc acc ctg act tgt gga acc aat cct ggc att ata aca aaa gca Phe Phe Thr Leu Thr Cys Gly Thr Asn Pro Gly Ile Ile Thr Lys Ala 35 40 45 aat gaa tta tta ttt ctt cat gtt tat gaa ttt gat gaa ktg atg ttt Asn Glu Leu Leu Phe Leu His Val Tyr Glu Phe Asp Glu Xaa Met Phe	111 159 207 255 303

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Ile Val Ser Thr Thr Phe Leu Val His Leu Val Val Met Ser Asp Leu 130 135 140	
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		_		2		-				aa L	eu S				hr Lys -20	
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Ya.	. ggc	, cgg	, 909	099	, ryg	Les	Mot	Pro	. yea	Tla	Dro	Ala Ala	Len	Glr	gag Glu	, , ,
Aac	. Эту	. wr	, wra	-15		, net			-10					~5		
acc	יאם:	ace	ו ממר			cas	aat	cac			даа	act	ago	_	gcc	750
300	- 3aı	. 500	- ששי	. 220		50	י שטי		, ,,,,,,	,	340				, ,,	. = •

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cgt cct tct atg gcc gct tca ggc act tct tgg ata tca tcg acc ctc Arg Pro Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Lev	- c 159
5 10 15 gea cac tet ttg tea etg aga gae gte tea gag agg etg tge age tge	
Ala His Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys 20 25 30	
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Arg Pro Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu
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WO 99/31236

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	Arg															
	40			•	-	45					50				•	
qtt	aaa	cta	qtq	gac	ttt	gga	rtc	akt	gct	cag	ctt	gat	cga	aca	gtg	444
Val	Lys	Leu	Val	Asp	Phe	Gly	Xaa	Xaa	Ala	Gln	Leu	Asp	Arg	Thr	Val	
55	•			-	60	_				65		_			70	
ggc	agg	arg	aat	act	ttc	att	gga	act	ccc	tac	tgg	atg	gca	cca	raa	492
	Arg															
•	_			75					80					85		
gtt	att	gcc	tgt	gat	gaa	aac	cca	sat	gcc	aca	tat	gat	ttc	aar	art	540
	Ile															
			90					95					100			
gac	ttg	tgg	tct	ttg	ggt	atc	acc	gcc	att	gaa	atg	gca	gaa	999	ctc	588
Asp	Leu	Trp	Ser	Leu	Gly	Ile	Thr	Ala	Ile	Glu	Met	Ala	Glu	Gly	Leu	
		105					110					115				
ccc	ctc	tct	gtg	aca	tgc	acc	cca	tga	gagc	tct	cttc	ctca	tc c	cccg	gaatc	642
Pro	Leu	Ser	Val	Thr	Cys	Thr	Pro									
	120					125										
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gct	tggt	aaa	aaat	caca	gc c	agcg	acca	g ca	acag	aaca	att	gatg	aag	catc	cattta	762
tac	gaga	cca	acct	aatg	ag c	gaca	ggtc	c gc	attc	aact	caa	ggac	cat	attg	atagaa	822
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<211> 644

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<222> 39..458

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<400> 369

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agg aac tgg ctg cca acc cct ccg gct acg ggc ccc tta ccg agc tcc Arg Asn Trp Leu Pro Thr Pro Pro Ala Thr Gly Pro Leu Pro Ser Ser 20 25 30	146
cag act ggt cat atg cgg atg gcc gcc ctg ctc ccc caa tgaaaggcca Gln Thr Gly His Met Arg Met Ala Ala Leu Leu Pro Gln 35 40 45	195
gcttcgaaaa aaagctgaaa gggagacktt tgcaaracra kttgtactgc tgtcacagga	255
aatggacgct ggattacaas catggcasct caggcagcar aakttgcagg aaraacaaag	315
aatggacgct ggattacaas tatggcastt taggcagaa aantgcaga ttagaaktaa	375
gaagcaggaa aatgctctta aacccaaagg ggcttcactg aaaascccac ttccaaktca	435
ataaaaagca actcctgcct cccttcctca ccctgtctct ggatttcttt tctatcacct	495
aratgettea tecagecara aaatageett cackkteece atetgtette arageaaaar	555
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ctcaggaggc tgaggcagga gaatcgctta aactcgggag gtagaggttg cagtgagcca	855
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aaa	918
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tct cat gcc cgc ttt tat ttc tta ttt cat cga cca tta agg ctg tta Ser His Ala Arg Phe Tyr Phe Leu Phe His Arg Pro Leu Arg Leu -20 -15 -10	97
aat ctg ctc atc ctt att gag ggc agt gtc gtc ttc tat cag ctc tat	145
Asn Leu Leu Ile Leu Ile Glu Gly Ser Val Val Phe Tyr Gln Leu Tyr -5 1 5	
tcc ttg ctg cgg tcg gag aag tgg aac cac aca ctt tcc atg gct ctc	193
Ser Leu Leu Arg Ser Glu Lys Trp Asn His Thr Leu Ser Met Ala Leu	
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atc ctc ttc tgc aac tac tat gtt tta ttt aaa ctt ctc cgg gac aga	241
Ile Leu Phe Cys Asn Tyr Tyr Val Leu Phe Lys Leu Leu Arg Asp Arg	
25 30 35 40	

wta kta tta ggc agg gca tac tcc tac cca ctc aac agt tat gaa ctc Xaa Xaa Leu Gly Arg Ala Tyr Ser Tyr Pro Leu Asn Ser Tyr Glu Leu	289
aag gca aac twa gct gcc tct caw caa tgagggagaa ctcagataaa Lys Ala Asn Xaa Ala Ala Ser Xaa Gln	336
aatattttca tacgttctat ttttttcttg tgatttttat aaatatttaa gatattttat attttgtata ctattatgtt ttgaaagtcg ggaagagtaa gggatattaa atgtatccgt aaacaaaaaa aaaaam	396 456 472
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tacacaaaa ata caa aaa ata att ttr att acc ggg gct agc agt ggc att	111
Met Arg Lys Val Val Leu Ile Thr Gly Ala Ser Ser Gly Ile	
-55 -50 -45 ggc ctg gcc ctc tgc aag cgg ctg ctg gcg gaa gat gat gag ctt cat	159
Gly Leu Ala Leu Cys Lys Arg Leu Leu Ala Glu Asp Asp Glu Leu His	
-40 -35 -30	207
ctg tgt ttg gcg tgc agg aat atg agc aag gca gaa gct gtc tgt gct Leu Cys Leu Ala Cys Arg Asn Met Ser Lys Ala Glu Ala Val Cys Ala	207
-25 -20 -15 -10	
get etg etg gee tet eac ecc act get gag gte acc att gte eag gtg	255
Ala Leu Leu Ala Ser His Pro Thr Ala Glu Val Thr Ile Val Gln Val	
gat gtc agc aac ctg cag tca ttc ttc cgg gcc tcc aag gaa ctt aag	303
Asp Val Ser Asn Leu Gln Ser Phe Phe Arg Ala Ser Lys Glu Leu Lys	
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caa agg ttt cag aga tta gac tgt ata tat cta aat gct ggg atc atg Gln Arg Phe Gln Arg Leu Asp Cys Ile Tyr Leu Asn Ala Gly Ile Met	332
25 30 ³⁵	
cct aat cca caa cta aat atc aaa gca ctt ttc ttt ggc ctc ttt tca	399
Pro Asn Pro Gln Leu Asn Ile Lys Ala Leu Phe Phe Gly Leu Phe Ser	
aga aaa gtg att cat atg ttc tcc aca gct gaa ggc ctg ctg acc cag	447
Arg Lys Val Ile His Met Phe Ser Thr Ala Glu Gly Leu Leu Thr Gln	
60 65 70	495
ggt gat aag atc act gct gat gga ctt cag gag gtg ttt gag acc aat Gly Asp Lys Ile Thr Ala Asp Gly Leu Gln Glu Val Phe Glu Thr Asn	
75 80 85	

gtc Val	ttt Phe	ggc Gly 90	cat His	ttt Phe	atc Ile	ctg Leu	att Ile 95	cgg Arg	gaa Glu	ctg Leu	gag Glu	cct Pro 100	ctc Leu	ctc Leu	tgt Cys	543
cac His	agt Ser 105	gac Asp	aat Asn	cca Pro	tct Ser	cag Gln 110	ctc Leu	atc Ile	tgg Trp	aca Thr	tca Ser 115	tct Ser	cgc Arg	agt Ser	gca Ala	591
Arg 120	Lys	Ser	Asn	Phe	Ser 125	Leu	Glu	Asp	Phe	Gln 130	His	Ser	Lys.	ggc Gly	Lys 135	639
			Ser											gtg Val 150		687
Leu	Asn	Arg	Asn 155	Phe	Asn	Gln	Gln	Gly 160	Leu	Tyr	Ser	Asn	Val 165	gcc Ala	Cys	735
cca Pro	ggt Gly	aca Thr 170	gca Ala,	ttg Leu	acc Thr	aat Asn	ttg Leu 175	aca Thr	tat Tyr	gga ·Gly	att Ile	ctg Leu 180	cct Pro	ccg Pro	ttt Phe	783
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														gta Val		879
														tat Tyr 230		927
														aag Lys		975
														ctg Leu		1023
														cag Gln		1071
		_			tgc Cys 285		taa	ttcc	agc a	actt	.ggga	ag go	ccaa	ggca	3	1122
aag	gate	act 1	tgaga	acca	gg ag	gttc	aaga	c cag	gcct	gaga	aaca	atagi	tga 🤉	gccct	ttgtct	1182
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ctc	agaa	gga	tgag	gtgg	ga gg	gatc	tctt	g ag	gctg	ggag	gcag	gaggi	ttg (cagt	gagctg	1302
															tgtata	1362
															accttc	1422
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atg	aact	atg a	aaaa	aaaa	aa aa	3										1504

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<213> Homo sapiens

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gttgataagg cgcttgctga tgacttggaa aaaaacttcc caagtttgaa ggttcagact

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697 757

765

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<222> 1027..1040

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tcactccaga tacatggaaa gatggtgcta ggaataccac agaaagtggt ggaagaaagc	180								
tgaatgaaaa taaagctttg acttcaaaaa aagccagaat tgatccata atg gaa gaa	238								
Met Glu Glu									
-25									
ata agt tot coa ott gta gaa tit gta aaa git tig igc acc aac cag	286								
Ile Ser Ser Pro Leu Val Glu Phe Val Lys Val Leu Cys Thr Asn Gln									
-20 -15 -10									
gtt ctc att act gcc agg gct gtg cct aca aaa aag gca tct gtg cga	334								
Val Leu Ile Thr Ala Arg Ala Val Pro Thr Lys Lys Ala Ser Val Arg									
-5 1 5									
tgt gtg gaa aaa agg ttt tgg ata cca aaa act aca agc aaa cat ctg	382								
Cys Val Glu Lys Arg Phe Trp Ile Pro Lys Thr Thr Ser Lys His Leu									
10 15 20 25									
tot aga tgt att gat gga att tot ggo ttt ota aat gat ttt act tto	430								
Ser Arg Cys Ile Asp Gly Ile Ser Gly Phe Leu Asn Asp Phe Thr Phe									
30 35 40									
tgc ctt gaa ttt tca agg cat aga tgt caa ctt aca gaa taacatgtkt	479								
Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu									
45 50									
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aaacagcaac agtgtaacta gtcttttgtt gtaaatggtt attttcctta taaaaatttt	599								
aaaaactaag tggcaaattc catgaaaata tttctcagtt ctgtatgcac ttttatttaa	659								
cattattcat ataattctcc ccccaccact ttatttat	719								
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atcaaagacc agttggattt atgatatttt ttatttgttc ttgcagccaa agtgccagtt	959								
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<222> 72..545

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<222> 72..203

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<221> polyA_site <222> 1151..1162

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Met Ala Gly Phe Leu Asp Asn Phe Arg Trp Pro Glu Cys

-40

-35

qaa tgt att gac tgg agt gag aga aga aat gct gtg qca tct gtt gtc

158

gaa tgt att gac tgg agt gag aga aga aat gct gtg gca tct gtt gtc
Glu Cys Ile Asp Trp Ser Glu Arg Arg Asn Ala Val Ala Ser Val Val

-30 -25 -20	
gca ggt ata ttg ttt ttt aca ggc tgg tgg ata atg att gat gca gc	t 206
Ala Gly Ile Leu Phe Phe Thr Gly Trp Trp Ile Met Ile Asp Ala Al	
-15 -10 -5 1	
gtg gtg tat cct aag cca gaa cag ttg aac cat gcc ttt cac aca tg	
Val Val Tyr Pro Lys Pro Glu Gln Leu Asn His Ala Phe His Thr Cy 5 10 15	rs
5 10 15 aggt gta ttt too aca ttg got tto tto atg ata aat got gta too aa	at 302
Gly Val Phe Ser Thr Leu Ala Phe Phe Met Ile Asn Ala Val Ser As	
20 25 30	
gct cag gtg aga ggt gat agc tat gaa agc ggc tgt tta gga aga ac	
Ala Gln Val Arg Gly Asp Ser Tyr Glu Ser Gly Cys Leu Gly Arg Th	ır
35 40 45	200
ggt gct cga gtt tgg ctt ttc att ggt ttc atg ttg atg ttt ggg tc	
Gly Ala Arg Val Trp Leu Phe Ile Gly Phe Met Leu Met Phe Gly Se 50 55 60 65	
ctt att gct tee atg tgg att ett ttt ggt gea tat gtt ace eaa aa	
Leu Ile Ala Ser Met Trp Ile Leu Phe Gly Ala Tyr Val Thr Gln As	sn
70 75 80	
act gat gtt tat ccg gga cta gct gtg ttt ttt caa aat gca ctt at	ta 494
Thr Asp Val Tyr Pro Gly Leu Ala Val Phe Phe Gln Asn Ala Leu Il	le
85 90 95	ga 542
ttt ttt agc act ctg atc tac aaa ttt gga aga acc gaa gag cta tg Phe Phe Ser Thr Leu Ile Tyr Lys Phe Gly Arg Thr Glu Glu Leu Tr	
100 105 110	-P
acc tgagatcact tottaagtca cattttcctt ttgttatatt ctgtttgtag	595
Thr	
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<222> 36..425

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<222> 1240..1250

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ctg cgc ttc ctg agg gct gac ggc gac ctg acg cta cta tgg gcc gag Leu Arg Phe Leu Arg Ala Asp Gly Asp Leu Thr Leu Leu Trp Ala Glu -5 1 5 10	149
tgg cag gga cga cgc cca gaa tgg gag ctg act gat atg gtg gtg tgg Trp Gln Gly Arg Arg Pro Glu Trp Glu Leu Thr Asp Met Val Val Trp 15 20 25	197
gtg act gga gcc tcg agt gga att ggt gag gag ctg gct tac cag ttg Val Thr Gly Ala Ser Ser Gly Ile Gly Glu Glu Leu Ala Tyr Gln Leu 30 35 40	245
tct aaa cta gga gtt tct ctt gtg ctg tca gcc aga aga gtg cat gag Ser Lys Leu Gly Val Ser Leu Val Leu Ser Ala Arg Arg Val His Glu 45 50 55	293
ctg gaa agg gtg aaa aga aga tgc cta gag aat ggc aat tta aaa gaa Leu Glu Arg Val Lys Arg Arg Cys Leu Glu Asn Gly Asn Leu Lys Glu 60 65 70	341
aaa gat ata ctt gtt ttg ccc ctt gac ctg acc gac act ggt tcc cat Lys Asp Ile Leu Val Leu Pro Leu Asp Leu Thr Asp Thr Gly Ser His 75 80 85 90	389
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<221> CDS

<222> 155..751

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tggtagaatc gacattctgg tcaacaatgg tgga atg tcc cag cgt tc	t ctg tgc 17	5									
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Leu Gly Thr Val Ser Leu Thr Lys Cys Val Leu Pro His Met	Ile Glu										
-35 -30	-25										
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Arg Lys Gln Gly Lys Ile Val Thr Val Asn Ser Ile Leu Gly											
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tot gta cot ott too att gga tao tgt got ago aag cat got	ctc cgg 36	7									
Ser Val Pro Leu Ser Ile Gly Tyr Cys Ala Ser Lys His Ala											
-5 1 5	-										
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Gly Phe Phe Asn Gly Leu Arg Thr Glu Leu Ala Thr Tyr Pro											
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Ile Val Ser Asn Ile Cys Pro Gly Pro Val Gln Ser Asn Ile											
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45 50 55	•										
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Gln Ser His Lys Met Thr Thr Ser Arg Cys Val Arg Leu Met											
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90 95 100	105										
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489

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585

621

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aac caa ktt gtc cta tgg gac aag att gtt ttg aga ggt gat aat ccg Asn Gln Xaa Val Leu Trp Asp Lys Ile Val Leu Arg Gly Asp Asn Pro

aag ctg ctg ctg aaa gat atg aaa aca aaa tat ttt ttc ttt gac gat

Lys Leu Leu Lys Asp Met Lys Thr Lys Tyr Phe Phe Phe Asp Asp

gga aat ggt ctc wag gga aac agg aat gtc act ttg acc ctg tct tgg
Gly Asn Gly Leu Xaa Gly Asn Arg Asn Val Thr Leu Thr Leu Ser Trp
110 115 120
aac gtc gta cca aat gct gga att cta cct ctt gtg aca gga tca gga

Asn Val Val Pro Asn Ala Gly Ile Leu Pro Leu Val Thr Gly Ser Gly

cac gta tot gto coa ttt coa gat aca tat gaa ata acg aag agt tat

His Val Ser Val Pro Phe Pro Asp Thr Tyr Glu Ile Thr Lys Ser Tyr

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85

150

105

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145

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Val Ser Arg Gly Arg Asp Ala Ala Gln Glu Leu Arg Ala Ser Leu Leu 70 65 Glu Thr Gln Met Glu Glu Asp Ile Leu Xaa Leu Gln Ala Xaa Ala Thr 85 80 Ala Glu Val Leu Gly Glu Val Ala Gln Ala Gln Lys Val Leu Arg Asp 100 95 105 Ser Val Gln Arg Leu Xaa Xaa Gln Leu Xaa Xaa Ala Trp Leu Gly Pro 115 120 Ala Tyr Arg Lys Phe Glu Val Leu Lys Ala Pro Pro Xaa Lys Gln Asn 130 135 His Ile Leu Trp Ala Leu Thr Gly His Val Xaa Arg Gln Xaa Arg Glu

145 Met Val Ala Gln Gln Xaa Xaa Leu Xaa Gln Ile Gln Glu Lys Leu His 160 165

150

Thr Ala Ala Leu Pro Ala 175

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~55 -50 ~45 Ser Gly Leu Ser Glu Val Val Glu Ala Ser Ser Leu Ser Trp Ser Thr -35 -30 -25 Arg Ile Lys Gly Phe Ile Ala Cys Phe Ala Ile Gly Ile Leu Cys Ser -20 -15 Leu Leu Gly Thr Val Leu Leu Trp Val Pro Arg Lys Gly Leu His Leu 1 Phe Ala Val Phe Tyr Thr Phe Gly Asn Ile Ala Ser Ile Gly Ser Thr 20 Ile Phe Leu Met Gly Pro Val Lys Gln Leu Lys Arg Met Phe Glu Pro 30 35 Thr Arg Leu Ile Ala Thr Ile Met Val Leu Leu Cys Phe Ala Leu Thr 50 45 Leu Cys Ser Ala Phe Trp Trp His Asn Lys Gly Leu Ala Leu Ile Phe 65 Cys Ile Leu Gln Ser Leu Ala Leu Thr Trp Tyr Ser Leu Ser Phe Ile 80 Pro Phe Ala Arg Asp Ala Val Lys Xaa Cys Phe Ala Val Cys Leu Ala 95 100

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<400> 383

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<210> 384 <211> 64 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 384

<222> -22..-1

Met Ile Ser Arg Gln Leu Arg Ser Leu Ser Cys Leu Cys Pro Ala Leu -20 -15 -10

Phe Bro Gly Thr Ser Ser Phe Ile Val Ala Leu Ser Ser Pro Ala Asp

<210> 385
<211> 27
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
<400> 385

Met Gly Phe Leu Xaa Leu Met Thr Leu Thr Thr His Val His Ser Ser -15 -10 -5 1

Ala Lys Pro Asn Glu Gln Pro Trp Leu Leu Asn 5 10

<210> 386 <211> 186 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

<400> 386 Met Ser Pro Ser Gly Arg Leu Cys Leu Leu Thr Ile Val Gly Leu Ile -15 -10 Leu Pro Thr Arg Gly Gln Thr Leu Lys Asp Thr Thr Ser Ser Ser 1 Ala Asp Ser Thr Ile Met Asp Ile Gln Val Pro Thr Arg Ala Pro Asp 20 Ala Val Tyr Thr Glu Leu Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro 35 30 Ala Asp Glu Thr Pro Gln Pro Gln Thr Gln Thr Gln Gln Leu Glu Gly 55 50 Thr Asp Gly Pro Leu Val Thr Asp Pro Glu Thr His Xaa Ser Xaa Lys 70 65 Ala Ala His Pro Thr Asp Asp Thr Thr Thr Leu Ser Glu Arg Pro Ser 85 Pro Ser Thr Xaa Val His Xaa Arg Pro Xaa Xaa Pro Ser Xaa His Leu 100 Val Phe Met Arg Met Thr Pro Ser Ser Met Met Asn Thr Pro Ser Gly 115 110 Asn Xaa Gly Cys Trp Ser Gln Leu Cys Cys Ser Ser Gln Ala Ser Ser 130 135 Ser Ser Pro Val Ala Ser Ala Gly Ser Cys Pro Gly Tyr Ala Gly Ile 145 Ile Ala Gly Glu Ser Ile Arg Asn Arg Ser 160

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<211> 179
<212> PRT
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<221> SIGNAL
<222> -26..-1
<400> 387
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                        -20
                                            -15
Leu Leu Cys Gly Pro Ser Gln Asp Gln Cys Arg Pro Val Leu Gln Asn
                    -5
Leu Leu Gln Ser Pro Gly Leu Thr Trp Ser Leu Glu Val Pro Thr Gly
                                15
Arg Glu Gly Lys Glu Gly Gly Asp Arg Gly Pro Gly Leu Xaa Gly Ala
Thr Pro Ala Arg Ser Pro Gln Gly Lys Glu Met Gly Arg Gln Arg Thr
Arg Lys Val Lys Gly Pro Ala Trp Xaa His Thr Ala Asn Gln Glu Leu
                    60
                                        65
Asn Arg Met Arg Ser Leu Ser Ser Gly Ser Val Pro Val Gly His Leu
                                    80
Glu Gly Gly Thr Val Lys Leu Gln Lys Asp Thr Gly Leu His Ser Cys
                                95
Xaa Asp Gly Met Ala Ser Leu Glu Gly Thr Pro Ala Ser Val Leu Ala
                            110
Asp Ala Cys Pro Gly Phe His Asp Val Xaa Val Gln Xaa Ala Leu Phe
                      125
                                           130
Gly Leu Ser Gly Xaa Xaa Leu Trp Leu Lys Thr His Phe Cys Leu Ser
135
                    140
Ile Xaa Leu
<210> 388
<211> 150
<212> PRT
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<222> -55..-1
<400> 388
Met Ala Thr Thr Val Pro Asp Gly Cys Arg Asn Gly Leu Lys Ser Lys
                    -50
                                        -45
Tyr Tyr Arg Leu Cys Asp Lys Ala Glu Ala Trp Gly Ile Val Leu Glu
                                     -30
Thr Val Ala Thr Ala Gly Val Val Thr Ser Val Ala Phe Met Leu Thr
                                 -15
Leu Pro Ile Leu Val Cys Lys Val Gln Asp Ser Asn Arg Arg Lys Met
Leu Pro Thr Gln Phe Leu Phe Leu Leu Gly Val Leu Gly Ile Phe Gly
                                        20
Leu Thr Phe Ala Phe Ile Ile Gly Leu Asp Gly Ser Thr Gly Pro Thr
                                    35
Arg Phe Phe Leu Phe Gly Ile Leu Phe Ser Ile Cys Phe Ser Cys Leu
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45 50 55
Leu Ala His Ala Val Ser Leu Thr Lys Leu Val Arg Gly Arg Lys Ala

<210> 389

<210> 390

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Pro Phe Pro Val Gly Asp Ser Gly Ser Gly Arg Gly Leu Gln Pro Ser 75 80 85

Pro Gly Cys Tyr Arg Tyr 90 95
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<211> 236
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -31..-1
<400> 389
Met Leu Ser Lys Gly Leu Lys Arg Lys Arg Glu Glu Glu Glu Lys
                                       -20
                      -25
Glu Pro Leu Ala Val Asp Ser Trp Trp Leu Asp Pro Gly His Ala Ala
                                   - 5
                  -10
Val Ala Gln Ala Pro Pro Ala Val Ala Ser Ser Ser Leu Phe Asp Leu
                          10
          5
Ser Val Leu Lys Leu His His Ser Leu Gln Xaa Ser Xaa Pro Asp Leu
                         25
Arg His Leu Val Leu Val Xaa Asn Thr Leu Arg Arg Ile Gln Ala Ser
                                        45
                      40
Met Ala Pro Ala Ala Ala Leu Pro Pro Val Pro Thr Pro Pro Ala Ala
                                    60
Pro Xaa Val Ala Asp Asn Leu Leu Ala Ser Ser Asp Ala Ala Leu Ser
                                 75
              70
Ala Ser Met Ala Xaa Leu Leu Glu Asp Leu Ser His Ile Glu Gly Leu
                                                95
                            90
          85
Ser Gln Ala Pro Gln Pro Leu Ala Asp Glu Gly Pro Pro Gly Arg Ser
      100
                         105
                                   110
Ile Gly Gly Xaa Pro Pro Xaa Leu Gly Ala Leu Asp Leu Leu Gly Pro
                                     125
                  120
Ala Thr Gly Cys Leu Leu Asp Asn Gly Leu Glu Gly Leu Phe Glu Asp
            135
                                   140
Ile Asp Thr Ser Met Tyr Asp Asn Glu Leu Trp Ala Pro Ala Ser Glu
                                 155
           150
Gly Leu Lys Pro Gly Pro Glu Asp Gly Pro Gly Lys Glu Glu Ala Pro
                             170
Glu Leu Asp Glu Ala Glu Leu Asp Tyr Leu Met Asp Val Leu Val Gly
                          185
Thr Gln Ala Leu Glu Arg Pro Pro Gly Pro Gly Arg
                     200
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<211> 149
<212> PRT
<213> Homo sapiens

<220>
<221> SIGNAL
<222> -100..-1

<400> 390
Met Glu Thr Leu Tyr Arg Val Pro Phe Leu Val Leu Glu Cys Pro Asn
-100 -95 -90 -85
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Leu Lys Leu Lys Lys Pro Pro Trp Leu His Met Pro Ser Ala Met Thr -75 -70 -80 Val Tyr Ala Leu Val Val Val Ser Tyr Phe Leu Ile Thr Gly Gly Ile -55 -60 Ile Tyr Asp Val Ile Val Glu Pro Pro Ser Val Gly Ser Met Thr Asp -45 -40 -50 Glu His Gly His Gln Arg Pro Val Ala Phe Leu Ala Tyr Arg Val Asn -25 -30 Gly Gln Tyr Ile Met Glu Gly Leu Ala Ser Ser Phe Leu Phe Thr Met -10 -15 -20 Gly Gly Leu Gly Phe Ile Ile Leu Asp Gly Ser Asn Ala Pro Asn Ile 5 Pro Lys Leu Asn Arg Phe Leu Leu Leu Phe Ile Gly Phe Val Cys Val 25 20 Leu Xaa Ser Phe Xaa Xaa Ala Arg Val Phe Met Arg Met Lys Leu Pro 35 Gly Tyr Leu Met Gly

<210> 391 <211> 69 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -49..-1

<210> 392 <211> 241 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -30..-1

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Cys Leu Trp Phe Arg Tyr Gly Ala His Gln Pro Glu Asn Leu Cys Leu 40 45 Asp Gly Cys Lys Ser Glu Ala Xaa Lys Phe Thr Val Arg Glu Ala Leu 60 Lys Glu Asn Gln Val Ser Leu Thr Val Asn Arg Val Thr Ser Asn Asp 75 Ser Ala Ile Tyr Ile Cys Gly Ile Ala Phe Pro Ser Val Pro Glu Ala 90 Arg Ala Lys Gln Thr Gly Gly Gly Thr Thr Leu Val Val Arg Glu Ile 105 110 Lys Leu Leu Ser Lys Glu Leu Arg Ser Phe Leu Thr Ala Leu Val Ser 125 130 120 Leu Leu Ser Val Tyr Val Thr Gly Val Cys Val Ala Phe Ile Leu Leu 135 140 Ser Lys Ser Lys Ser Asn Pro Leu Arg Asn Lys Glu Ile Lys Glu Asp 150 155 Ser Gln Lys Lys Lys Ser Ala Arg Arg Ile Phe Gln Glu Ile Ala Gln . 170 175 Glu Leu Tyr His Lys Arg His Val Glu Thr Asn Gln Gln Ser Glu Lys 185 190 Asp Asn Asn Thr Tyr Glu Asn Arg Arg Val Leu Ser Asn Tyr Glu Arg 200 205 : 210 Pro

<210> 393 <211> 47 <212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -30..-1

<400> 393

<210> 394 <211> 65 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -28..-1

<400> 394 Met Ala Ph

Met Ala Phe Gly Leu Gln Met Phe Ile Gln Arg Lys Phe Pro Tyr Pro -25 | -25 | -20 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -25 | -2

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35

Ser

<210> 395

<211> 73

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -24..-1

<400> 395

Met Thr Cys Trp Met Leu Pro Pro Ile Ser Phe Leu Ser Tyr Leu Pro
-20
-15
-10

Leu Trp Leu Gly Pro Ile Trp Pro Cys Ser Gly Ser Thr Leu Gly Lys
-5 5

Pro Asp Pro Gly Val Trp Pro Ser Leu Phe Arg Pro Trp Asp Ala Ala 10 15 20

Ser Pro Gly Asn Tyr Ala Leu Ser Arg Gly Xaa Asn Xaa Tyr Xaa Xaa 25 30 35 40

Trp Gly Gln Gly Thr His Ser Ser Leu

45

<210> 396

<211> 60

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -18..-1

<400> 396

Met Pro Cys Pro Thr Trp Thr Cys Leu Lys Ser Phe Pro Ser Pro Thr
-15 -10 -5

Ser Ser His Ala Ser Ser Leu His Leu Pro Pro Ser Cys Thr Arg Leu

Thr Leu Thr Gln Thr Leu Arg Thr Gly Met His Leu Ser Arg Ala Leu
15 20 25 30

25 Gln Gly Thr Leu Thr Arg Leu Gln Ser Thr Pro Ala

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<210> 397

<211> 192

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -93..-1

<400> 397

Met Ala Glu Leu Gly Leu Asn Glu His His Gln Asn Glu Val Ile Asn
-90
-85
-80

Tyr Met Arg Phe Ala Arg Ser Lys Arg Gly Leu Arg Leu Lys Thr Val

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-70
Asp Ser Cys Phe Gln Asp Leu Lys Glu Ser Arg Leu Val Glu Asp Thr
                       -55
Phe Thr Ile Asp Glu Val Ser Glu Val Leu Asn Gly Leu Gln Ala Val
                   -40
                                       -35
Val His Ser Glu Val Glu Ser Glu Leu Ile Asn Thr Ala Tyr Thr Asn
                                   -20
Val Leu Leu Arg Gln Leu Phe Ala Gln Ala Glu Lys Trp Tyr Leu
                              -5
Lys Leu Gln Thr Asp Ile Ser Glu Leu Glu Asn Arg Glu Leu Leu Glu
                                          15
                      10
Gln Xaa Ala Glu Phe Glu Lys Ala Xaa Ile Thr Ser Ser Asn Lys Lys
                  25
                                      30
Pro Ile Leu Xaa Val Thr Xaa Pro Lys Leu Ala Pro Leu Asn Glu Gly
Gly Thr Ala Lys Leu Leu Asn Lys Val Ile Cys Ile Ile Leu Arg Asn
                               60
Gly Lys Ser Leu Ile Leu Ser Cys His Cys Leu Gly Trp Arg Asn Lys
                          75
Ser Gly Arg Phe Val Ser Gly Pro Leu Arg Ile Ile Ser Pro Leu Gln
                      90
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<400> 398 Met Asn Leu Phe Ile Met Tyr Met Ala Gly Asn Thr Ile Ser Ile Phe

Pro Thr Met Met Val Cys Met Met Ala Trp Arg Pro Ile Gln Ala Leu -50 -45 Met Ala Ile Ser Ala Thr Phe Lys Met Leu Glu Ser Ser Ser Gln Lys -35 -30 Phe Leu Gln Gly Leu Val Tyr Leu Ile Gly Asn Leu Met Gly Leu Ala -15 -20 Leu Ala Val Tyr Lys Cys Gln Ser Met Gly Leu Leu Pro Thr His Ala 1 - 5 Ser Asp Trp Leu Ala Phe Ile Glu Pro Pro Glu Arg Met Glu Ser Val Val Glu Asp Cys Phe Cys Glu His Glu Lys Ala Ala Pro Gly Pro Tyr 35 Val Phe Gly Ser Tyr Leu His Pro Ser Leu Ser Pro Val Ala Pro Gln 50 His Thr Leu Lys Leu Ile Thr Tyr Val Lys Lys Asn Gln Lys Thr Leu Phe Ser Met Val Gly

<210> 399 <211> 73 <212> PRT

75

<213> Homo sapiens

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<220>
<221> SIGNAL
<222> -20..-1
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<210> 400 <211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -20..-1

<400> 400

Met Asn Leu His Phe Pro Gln Trp Phe Val His Ser Ser Ala Leu Gly -15 -10 Leu Val Leu Ala Pro Pro Phe Ser Ser Pro Gly Thr Asp Pro Thr Phe 5 Pro Cys Ile Tyr Cys Arg Leu Leu Asn Met Ile Met Thr Arg Leu Ala 15 20 25 Phe Ser Phe Ile Thr Cys Leu Cys Pro Asn Leu Lys Glu Val Cys Leu 35 40 Ile Leu Pro Glu Lys Asn Cys Asn Ser Arg His Ala Gly Phe Val Gly 50 55 Pro Xaa Lys Leu Arg Gln

<210> 401 <211> 78 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

Met Cys Pro Val Phe Ser Lys Gln Leu Leu Ala Cys Gly Ser Leu Leu
-20 -15 -10

Pro Gly Leu Trp Gln His Leu Thr Ala Asn His Trp Pro Pro Phe Ser
-5 1 5 10

Xaa Phe Leu Cys Thr Val Cys Ser Gly Ser Ser Glu Gln Ile Ser Glu
15 20 25

Tyr Thr Ala Ser Ala Thr Pro Pro Leu Cys Arg Ser Leu Asn Gln Glu
30 35 40

Pro Phe Val Ser Arg Ala Ile Arg Pro Lys Tyr Ser Ile Thr

.45

50

55

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<210> 402
<211> 65
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -28..-1
<400> 402
Met Gly Lys Gly His Gln Arg Pro Trp Trp Lys Val Leu Pro Leu Ser
       -25 -20 -15
Cys Phe Leu Val Ala Leu Ile Ile Trp Cys Tyr Leu Arg Glu Glu Ser
                        -5
Glu Ala Asp Gln Trp Leu Arg Gln Val Trp Gly Glu Val Pro Glu Pro
                        15
        10
Ser Asp Arg Ser Glu Glu Pro Glu Thr Pro Ala Ala Tyr Arg Ala Arg
Thr
<210> 403
<211> 211
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<211> 211
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -27..-1

<400> 403

-20 Phe Phe Ser Gly Val. Tyr Gly Thr Cys Ile Gly Ala Thr Asn Lys Phe 1 -5 Gly Ala Glu Glu Xaa Ser Leu Ile Gly Leu Ser Gly Ile Phe Ile Gly 10 15 Ile Gly Glu Ile Leu Gly Gly Ser Leu Phe Gly Leu Leu Ser Lys Asn 30 Asn Arg Phe Gly Arg Asn Pro Val Val Leu Leu Gly Ile Leu Val His 45 50 Phe Ile Ala Phe Tyr Leu Ile Phe Leu Asn Met Pro Gly Asp Ala Pro 65 60 Ile Ala Pro Val Lys Gly Thr Asp Ser Ser Ala Tyr Ile Lys Ser Ser 75 80 Lys Xaa Phe Ala Ile Leu Cys Xaa Phe Leu Xaa Gly Leu Gly Asn Ser 95 90 Cys Phe Asn Thr Xaa Leu Leu Xaa Ile Xaa Gly Phe Leu Tyr Ser Glu 115 110 Xaa Ser Ala Pro Xaa Phe Ala Ile Phe Asn Phe Val Gln Ser Ile Cys 120 125 130 Ala Ala Val Ala Phe Phe Tyr Ser Asn Tyr Leu Leu Leu His Trp Gln 135 140 145 Leu Leu Val Met Val Ile Phe Gly Phe Xaa Gly Thr Ile Ser Phe Phe 150 . 155 160 Thr Val Glu Trp Glu Xaa Ala Ala Phe Val Xaa Arg Gly Ser Asp Tyr 170 175

Met Leu Leu Ser Ile Thr Thr Ala Tyr Thr Gly Leu Glu Leu Thr

Arg Ser Ile

<210> 404 <211> 123 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -80..-1

<400> 404 Met Ser Thr Trp Tyr Leu Ala Leu Asn Lys Ser Tyr Lys Asn Lys Asp **-80 -75 -70** Ser Val Arg Ile Tyr Leu Ser Leu Cys Thr Val Ser Ile Lys Phe Thr -55 .-60 Tyr Phe His Asp Ile Gln Thr Asn Cys Leu Thr Thr Trp Lys His Ser -45 -40 Arg Cys Arg Phe Tyr Trp Ala Phe Gly Gly Ser Ile Leu Gln His Ser -20 -30 -25 Val Asp Pro Leu Val Leu Phe Leu Ser Leu Ala Leu Leu Val Thr Pro -15 -10 -5 Thr Ser Thr Pro Ser Ala Lys Ile Gln Ser Leu Gln Ile Asp Leu Pro 1 5 10 15 Gly Gly Trp Arg Leu Ala Thr Asp Arg Ile Phe Thr Leu Ser Pro Val 20 25 Pro Met Asp Xaa Pro Leu Ile Leu His Gln Leu 35 40

<210> 405 <211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -26..-1 <400> 405

Met Glu Lys Ser Trp Met Leu Trp Asn Phe Val Glu Arg Trp Leu Ile -25 -20 -15 Ala Leu Ala Ser Trp Ser Trp Ala Leu Cys Arg Ile Ser Leu Leu Pro -5 1 Leu Ile Val Thr Phe His Leu Tyr Gly Gly Ile Ile Leu Leu Leu 10 15 Ile Phe Ile Ser Ile Xaa Gly Ile Leu Tyr Lys Phe Xaa Asp Val Leu 25 30 Leu Tyr Phe Pro Xaa Gln Xaa Ser Ser Ser Arg Leu Tyr Asp Ser His 40 45 50 Ala His Trp Xaa Ser Xaa

<210> 406 <211> 162 <212> PRT <213> Homo sapiens

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<220>
<221> SIGNAL
<222> -31..-1
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<400> 406 Met Ala Ala Arp Pro Ser Gly Pro Xaa Ala Pro Glu Ala Val Thr -20 -25 Ala Arg Leu Val Gly Val Leu Trp Phe Val Ser Val Thr Thr Gly Pro -10 -5 Trp Gly Ala Val Ala Thr Ser Ala Gly Gly Glu Glu Ser Leu Lys Cys 10 Glu Asp Leu Lys Val Gly Gln Tyr Ile Cys Lys Asp Pro Lys Ile Asn 25 Asp Ala Thr Gln Glu Pro Val Asn Cys Thr Asn Tyr Thr Ala His Val 35 40 45 Ser Cys Phe Pro Ala Pro Asn Ile Thr Cys Lys Asp Ser Ser Gly Asn 55 60 Glu Thr His Phe Thr Gly Asn Glu Val Gly Phe Phe Lys Pro Ile Ser 70 75 Cys Arg Asn Val Asn Gly Tyr Ser Tyr Asn Glu Gln Ser His Val Ser 90 Phe Ser Trp Met Val Gly Ser Arg Ser Ile Leu Pro Trp Ile Pro Cys 105 Phe Gly Phe Val Lys Xaa Xaa His Cys Arg Val Xaa Trp Asn Trp Glu 120 125

<210> 407 <211> 98 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -37..-1

Pro Asn 130

<400> 407 Met Ala Ser Leu Leu Cys Cys Gly Pro Lys Leu Ala Ala Cys Gly Ile -30 Val Leu Ser Ala Trp Gly Val Ile Met Leu Ile Met Leu Gly Ile Phe -20 · -15 -10 Phe Asn Val His Ser Ala Val Leu Ile Glu Asp Val Pro Phe Thr Glu 1 Lys Asp Phe Glu Asn Gly Pro Gln Asn Ile Tyr Asn Leu Tyr Xaa Gln 20 15 Xaa Ser Tyr Asn Cys Phe Ile Ala Ala Gly Leu Tyr Leu Leu Leu Gly 35 Gly Phe Ser Phe Cys Gln Xaa Arg Leu Asn Lys Arg Lys Glu Tyr Met Val Arg 60

<210> 408 <211> 70 <212> PRT <213> Homo sapiens

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<220>
<221> SIGNAL
<222> -15..-1
<400> 408
Met Arg Phe Leu Pro Cys Cys Leu Leu Trp Ser Val Phe Asn Pro Glu
      -10
                        -5
Ser Leu Asn Cys His Tyr Phe Xaa Xaa Glu Xaa Cys Ile Phe Xaa Ser
                            10
Leu Gln Tyr Tyr Glu Ile Ser Leu Gln Glu Lys Leu Leu Gly Phe Leu
                      25
Trp Leu Cys Phe Leu Ser Tyr Phe Phe Arg Ala Val Tyr Phe Leu Ile
                 40
Asp Phe Ser Ser Phe Thr
50
<210> 409
<211> 60
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -45..-1
<400> 409
Met His Ser Leu Phe Ile Ala Ser Leu Lys Val Leu Phe Tyr Tyr Ser
                 -40
                                    -35
Phe Ser Phe Arg Phe Asn Trp Phe Asp Cys Leu Leu His Asn Leu Gly
             -25
                                -20
Glu Asn Phe Leu Ser Leu Leu Ser Lys Ser Cys Ser Ala Asp Pro Ser
        -10
                            -5
Gly Ser Thr Phe Met Arg Asp Ile Glu Thr Asn Lys
                     10
<210> 410
<211> 39
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -22..-1
<400> 410
Met Pro Glu Ala Val Glu Gln Ser Ala His Leu Phe Val Thr Trp Ser
                     ~15
                                    -10
Ser Gln Arg Ala Leu Ser His Pro Ala Pro Phe Leu Thr Xaa Xaa Lys
  -5
                    1
                                    5
Asn Pro Phe Leu Trp Lys Leu
```

<210> 411 <211> 51 <212> PRT

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<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 411
Met Ala Phe Gln Ser Leu Leu Glu Met Lys Phe Phe Leu Cys Ala Ala
                                                   -10
           -20
                               -15
Phe Pro Leu Gly Ala Gly Val Lys Met Phe His Tyr Leu Gly Pro Gly
                          1
Lys Pro Leu Xaa Gln Ala Ser Pro Ser Pro His Pro His Arg Xaa Arg
                   15
                                        20
Ile Trp Pro
<210> 412
<211> 95
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<212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -48..-1 <400> 412 Met Ala Ser Ser His Trp Asn Glu Thr Thr Thr Ser Val Tyr Gln Tyr -45 -40 Leu Gly Phe Gln Val Gln Lys Ile Tyr Pro Phe His Asp Asn Trp Asn -25 -20 -30 Thr Ala Cys Phe Val Ile Leu Leu Leu Phe Ile Phe Thr Val Val Ser -10 -5 Leu Val Val Leu Ala Phe Leu Tyr Glu Val Leu Xaa Xaa Cys Cys

1 5 10 15

Val Lys Asn Lys Thr Val Lys Asp Leu Lys Ser Glu Pro Asn Pro Leu
20 25 30

Xaa Xaa Met Met Asp Asn Ile Arg Lys Arg Glu Thr Glu Val Val

Xaa Xaa Met Met Asp Asn Ile Arg Lys Arg Glu Thr Glu Val Val 35 40 45

<210> 413
<211> 60
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -32..-1

<210> 414

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<211> 170
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -79..-1
<400> 414
Met Glu Asp Pro Asn Pro Glu Glu Asn Met Lys Gln Gln Asp Ser Pro
              -75
                              -70
Lys Glu Arg Ser Pro Gln Ser Pro Gly Gly Asn Ile Cys His Leu Gly
                            -55
           -60
Ala Pro Lys Cys Thr Arg Cys Leu Ile Thr Phe Ala Asp Ser Lys Phe
       -45
                          -40
                                          -35
Gln Glu Arg His Met Lys Arg Glu His Pro Ala Asp Phe Val Ala Gln
                       -25
                                         -20
Lys Leu Gln Gly Val Leu Phe Ile Cys Phe Thr Cys Ala Arg Ser Phe
                -10
                                   -5
Pro Ser Ser Lys Ala Xaa Xaa Thr His Gln Arg Ser His Gly Pro Xaa
                            10 15
Ala Lys Pro Thr Leu Pro Val Ala Thr Thr Thr Ala Gln Pro Thr Phe
                         25
                                          30
Pro Cys Pro Asp Cys Gly Lys Thr Phe Gly Gln Ala Val Ser Leu Xaa
                     40
                                         45
Arg His Xaa Gln Xaa His Glu Val Arg Ala Pro Pro Gly Thr Phe Ala
                  55
                                     60
Cys Thr Xaa Cys Gly Gln Asp Phe Ala Gln Glu Xaa Gly Leu His Gln
              70
                                 75
His Tyr Ile Arg His Ala Arg Gly Gly Leu
           85
```

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<210> 415
<211> 190
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -82..-1
<400> 415
Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe
                           -75
                                              -70
His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly
   -65
                       -60
                                          -55
Val Ser Leu Pro Gly Ile Leu Ala Ala Lys Cys Gly Ala Glu Val Ile
                   -45
                                       -40
Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln
               -30
                                   -25
Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu Thr
           -15
                               -10
                                                  - 5
Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile
                       5
                                          10
Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Xaa Phe Glu Asp Ile
                  20
                                      25
Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln Leu
                                   40
```

Trp Ser Thr Tyr Gln Val Arg Xaa Ala Asp Trp Ser Leu Glu Ala Leu 55 50 Leu Tyr Lys Trp Asp Met Lys Cys Val His Ile Pro Leu Glu Ser Phe 70 75 Asp Ala Asp Lys Glu Xaa Ile Ala Glu Ser Thr Leu Pro Gly Arg His 85 Thr Val Glu Met Leu Val Ile Ser Phe Ala Lys Asp Ser Leu

<210> 416 <211> 114 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1

<400> 416

Met Met Ala Ala Val Pro Pro Gly Leu Glu Pro Trp Asn Arg Val Arg -60 -55 -50 Ile Pro Lys Ala Gly Asn Arg Ser Ala Val Thr Val Gln Asn Pro Gly -40 -30 -35 Ala Ala Leu Asp Leu Cys Ile Ala Ala Val Ile Lys Glu Cys His Leu -25 -20 -15 Val Ile Leu Ser Leu Lys Ser Gln Thr Leu Asp Ala Glu Thr Asp Val -5 Leu Cys Ala Val Leu Tyr Ser Asn His Asn Arg Met Gly Arg His Lys 10 15 Pro His Leu Ala Leu Lys Gln Val Glu Gln Cys Leu Lys Arg Leu Lys 25 30 Asn Met Asn Leu Glu Gly Ser Ile Gln Asp Leu Phe Glu Leu Phe Ser 40 -45 Ser Lys

<210> 417 <211> 161 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -108..-1

<400> 417 Met Thr Ser Gly Gln Ala Arg Ala Ser Xaa Gln Ser Pro Gln Ala Leu -100 -95 -105 Glu Asp Ser Gly Pro Val Asn Ile Ser Val Ser Ile Thr Leu Thr Leu -90 -85 -80 Asp Pro Leu Lys Pro Phe Gly Gly Tyr Ser Arg Asn Val Thr His Leu -70 -65 Tyr Ser Thr Ile Leu Gly His Gln Ile Gly Leu Ser Gly Arg Glu Ala -55 -50 His Glu Glu Ile Asn Ile Thr Phe Thr Leu Pro Thr Ala Trp Ser Ser -40 -35 -30 Asp Asp Cys Ala Leu His Gly His Cys Glu Gln Val Val Phe Thr Ala -20 -25 Cys Met Thr Leu Thr Ala Ser Pro Gly Val Phe Pro Ser Leu Tyr Ser

```
-10
                            - 5
His Arg Thr Val Phe Leu Thr Arg Thr Ala Thr Pro Arg Ser Gly Thr
                    10
                                    . 15
Arg Ser Ser Gln Leu Pro Glu Met Pro Thr Gln Asn Thr Pro Lys Ile
                                    30
Thr Ile Leu Ser Gly Val Ile Arg Gly Pro Leu Glu Lys Ser Ile Met
                              45
Leu
<210> 418
<211> 67
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 418
Met Leu Gly Gly Asp His Arg Ala Leu Leu Leu Lys Ile Trp Leu Leu
                        -15
                                            -10
Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro Gly Arg Leu Val Val
Met Glu Arg Arg Val Lys Asn Asp Leu Met Ser Phe Leu Ser Thr Val
          15
                                20
Leu Leu Ser Phe His Ser Ser Asn Ala Arg Val Ser His Cys Glu Pro
                            35
Leu Arg Met
   45
<210> 419
<211> 332
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -32..-1
<400> 419
Met Ile Xaa Leu Arg Asp Thr Ala Ala Ser Leu Arg Leu Glu Arg Asp
       -30
                            -25
                                               -20
Thr Arg Gln Leu Pro Leu Leu Thr Ser Ala Leu His Gly Leu Gln Gln
  -15
                        -10
                                          - 5
Gln His Pro Ala Phe Ser Gly Val Ala Arg Leu Ala Lys Arg Trp Val
                                    10
Arg Ala Gln Leu Leu Gly Glu Gly Phe Ala Asp Glu Ser Leu Asp Leu
                                25
Val Ala Ala Leu Phe Leu His Pro Glu Pro Phe Thr Pro Pro Ser
```

Ser Pro Gln Val Gly Phe Leu Arg Phe Leu Phe Leu Val Ser Thr Phe 50

Asp Trp Lys Asn Asn Pro Leu Phe Val Asn Leu Asn Asn Glu Leu Thr 65

Val Glu Glu Gln Val Glu Ile Arg Ser Gly Phe Leu Ala Ala Arg Ala 85

Gln Leu Pro Val Met Val Ile Val Thr Pro Gln Xaa Arg Lys Asn Ser 100

100

Val Trp Thr Gln Asp Gly Pro Ser Ala Gln Ile Leu Gln Gln Leu Val 120 125 Val Leu Ala Ala Glu Xaa Leu Pro Met Leu Xaa Xaa Gln Leu Met Asp 140 135 Pro Arg Gly Pro Gly Asp Ile Arg Thr Xaa Phe Arg Pro Pro Leu Asp 150 155 Ile Tyr Asp Val Leu Ile Arg Leu Ser Pro Arg His Ile Pro Arg His 170 165 Arg Gln Ala Val Asp Ser Pro Ala Ala Ser Phe Cys Arg Gly Leu Leu 185 190 180 Ser Gln Pro Gly Pro Ser Ser Leu Met Pro Val Leu Gly Xaa Asp Pro 200 205 195 Pro Gln Leu Tyr Leu Thr Gln Leu Xaa Glu Ala Phe Gly Asp Leu Ala 215 220 Leu Phe Phe Tyr Asp Gln His Gly Gly Glu Val Ile Gly Val Leu Trp 235 230 Lys Pro Thr Ser Phe Gln Pro Gln Pro Phe Lys Ala Ser Ser Thr Lys 250 245 Gly Arg Met Val Met Ser Arg Gly Glu Leu Val Met Val Pro Asn 265 Val Glu Ala Ile Leu Glu Asp Phe Ala Val Leu Gly Glu Gly Leu Val 280 Gln Thr Val Glu Ala Arg Ser Glu Arg Trp Thr Val 290 295

<210> 420 <211> 65 <212> PRT <213> Homo sapiens

<220>
<221> SIGNAL
<222> -19..-1

<400> 420

<210> 421 <211> 57 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -30..-1

<400> 421

Met Pro Thr Gly Lys Gln Leu Ala Asp Ile Gly Tyr Lys Thr Phe Ser
-30 -25 -20 -15
Thr Ser Met Met Leu Leu Thr Val Tyr Gly Gly Tyr Leu Cys Ser Val

```
-10
                                   -5
Arg Val Tyr His Tyr Phe Gln Trp Arg Arg Ala Gln Arg Gln Ala Ala
                       10
Glu Glu Gln Lys Xaa Ser Gly Ile Met
<210> 422
<211> 85
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
<400> 422
Met Lys Lys Val Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val
                         -10
Gly Phe Pro Val Ser Gln Asp Gln Glu Arg Glu Lys Arg Ser Ile Ser
   1 5
                                      10
Asp Ser Asp Glu Leu Ala Ser Gly Xaa Phe Val Phe Pro Tyr Pro Tyr
              20
                                25
Pro Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe
                              40
          35
Arg Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro Thr Thr Pro
Leu Pro Ser Glu Lys
   65
<210> 423
<211> 85
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
Met Lys Lys Val Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val
      -15
                           -10
Gly Phe Pro Val Ser Gln Asp Xaa Glu Arg Glu Lys Arg Ser Ile Ser
   1
                  5
Asp Ser Asp Glu Leu Ala Ser Gly Phe Phe Val Phe Pro Tyr Pro Tyr
               20
                                   25
Pro Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe
                               40
Arg Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro Thr Thr Pro
Leu Pro Ser Glu Lys
    65
<210> 424
<211> 69
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<212> PRT

<213> Homo sapiens

<210> 425 <211> 122 <212> PRT

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<220>
<221> SIGNAL
<222> -29..-1
<400> 424
Met Thr Cys Arg Gly Ser Cys Ser Tyr Ala Thr Arg Arg Ser Pro Ser
            -25 -20 -15
Glu Leu Ser Leu Leu Pro Ser Ser Leu Trp Val Leu Ala Thr Ser Ser
                           -5
    -10
Pro Thr Ile Thr Ile Ala Leu Ala Met Ala Ala Gly Asn Leu Cys Pro
                                      15
                 10
Leu Pro Ser Ser Xaa Arg Xaa Lys Arg Arg Trp Cys Gln Ala Xaa Gln
                                  30
          25
Gln Xaa Ala Leu Leu
```

<213> Homo sapiens <220> <221> SIGNAL <222> -56..-1 <400> 425 Met Val Pro Trp Pro Arg Gly Lys Val Lys Thr Ala Pro Ile Pro Ile -50 -45 Ser Arg Phe Pro Phe Leu Pro Thr His Asp Pro Pro Thr Pro Ala His -30 -35 Trp Ser Pro Ala Ser His Gln Gln Phe Lys His Xaa Ser Pro Leu Leu -20 -15 Thr Leu Ala Leu Leu Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys 1 5 Lys Leu Ala Gly Gln Lys Ala Lys Lys Leu Pro Ser Phe Ser Ser Leu 20 15 10 Pro Leu Thr Leu Trp Pro Leu Thr Pro Gln Phe Ala Glu Leu Thr Thr 35 30 Val Ala Gln Lys Lys Leu Arg Trp Ser Gly Thr Leu Gly Trp Gly Pro 45 50

Val Pro Ser Trp Val Gln Phe Phe Leu Gly

60

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Arg Cys Ser Gly Ser Pro Leu Pro Leu
5 10
```

<210> 427 <211> 50 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -36..-1 <400> 427 Met Ala Pro His Thr Ala Ser Phe Gly Val Cys Pro Leu Leu Ser Val -30 -25 Thr Arg Val Val Ala Thr Glu His Trp Leu Phe Leu Ala Ser Leu Ser -20 -15 -10 Gly Ile Lys Thr Tyr Gln Ser Tyr Ile Ser Val Phe Cys Lys Val Thr 1 5 Leu Ile

<210> 428
<211> 136
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1

<400> 428

Met Asp Ser Leu Arg Lys Met Leu Ile Ser Val Ala Met Leu Gly Ala -15 -10 Xaa Ala Gly Val Gly Tyr Ala Leu Leu Val Ile Val Thr Pro Gly Glu Arg Arg Lys Gln Glu Met Leu Lys Glu Met Pro Leu Gln Asp Pro Arg - 20 25 Ser Arg Glu Glu Ala Ala Arg Thr Gln Gln Leu Leu Leu Ala Thr Leu 40 Gln Glu Ala Ala Thr Thr Gln Glu Asn Val Ala Trp Arg Lys Asn Trp 50 55 Met Val Gly Gly Glu Gly Gly Ala Thr Gly Xaa His Arg Glu Thr Gly 70 Leu Ala Ser Val Gly Ala Gly Pro Trp Leu Gly Arg Arg Asn Pro Arg 85 90 Gln Leu Ser Pro Ser Trp Ala Xaa Arg Lys Ile Arg Xaa Glu Asn Xaa 95 100 105 Met Pro Gly Leu Ser Gly Val Leu 115

<210> 429 <211> 194 <212> PRT <213> Homo sapiens

<220>

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<221> SIGNAL <222> -65..-1
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<400> 429 Met Gln Asp Ala Pro Leu Ser Cys Leu Ser Pro Thr Lys Trp Ser Ser -60 **-**55 Val Ser Ser Ala Asp Ser Thr Glu Lys Ser Ala Ser Ala Ala Gly Thr -45 -40 Arg Asn Leu Pro Phe Gln Phe Cys Leu Arg Gln Ala Leu Arg Met Lys -25 -30 Ala Ala Gly Ile Leu Thr Leu Ile Gly Cys Leu Val Thr Gly Val Glu -10 Ser Lys Ile Tyr Thr Arg Cys Lys Leu Ala Lys Ile Phe Ser Arg Ala 10 Gly Leu Asp Asn Xaa Arg Gly Phe Ser Leu Gly Asn Trp Ile Cys Met 25 Ala Tyr Tyr Glu Ser Gly Tyr Asn Thr Thr Ala Gln Thr Val Leu Asp 40 Asp Gly Ser Ile Asp Tyr Gly Ile Phe Gln Ile Asn Ser Phe Ala Trp 55 60 Cys Arg Arg Gly Lys Leu Lys Glu Asn Asn His Cys His Val Ala Cys 70 75 Ser Ala Leu Xaa Thr Asp Asp Leu Thr Asp Ala Ile Ile Cys Ala Xaa 85 Lys Ile Val Lys Glu Thr Gln Gly Met Asn Tyr Trp Gln Gly Trp Lys 105 110 Lys His Cys Glu Gly Arg Asp Leu Ser Xaa Trp Lys Lys Gly Cys Glu 120 Val Ser

<210> 430 <211> 141 <212> PRT <213> Homo sapiens

<220>
<221> SIGNAL
<222> -69..-1

<400> 430 Met Thr Ser Gln Pro Val Pro Asn Glu Thr Ile Ile Val Leu Pro Ser

-65 -60 Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln -50 -45 Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Ile Lys Val Ile -30 -25 -35 Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile -10 -15 Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser 1 Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Phe Phe Val Xaa 20 Lys Xaa Ser Glu Glu Gly Arg Met Gly Gln Xaa Gly Glu Glu Xaa Xaa 35 40 Asn Ser Leu Asn Phe Pro Xaa Ala Ser Leu Leu Xaa Leu Ile Cys Gln 50 Xaa Gln Gly Phe Asn Gly Glu Ser Cys Ser Pro Val Gly 65

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<210> 431
<211> 248
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -69..-1
<400> 431
Met Thr Ser Gln Pro Val Pro Asn Glu Thr Ile Ile Val Leu Pro Ser
                -65
                                    -60
Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln
            -50
                                -45
Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Xaa Lys Val Ile
        -35 🔻
                           -30
Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile
                       -15
                                        -10
Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser
                  1
Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Phe Phe Phe Ile
          15
Ile Ser Gly Ser Leu Ser Ile Ala Thr Lys Lys Arg Leu Thr Asn Leu
       3.0
                           35
Leu Val His Thr Thr Leu Val Gly Ser Ile Leu Ser Ala Leu Ser Ala
                       50
                                           55
Leu Val Gly Phe Ile Xaa Leu Ser Val Lys Gln Ala Thr Leu Asn Pro
                   65
                                       70 -
Ala Ser Leu Xaa Cys Glu Leu Xaa Lys Asn Asn Ile Pro Thr Xaa Xaa
                                   85
Tyr Val Xaa Tyr Phe Tyr His Asp Ser Leu Tyr Thr Thr Asp Xaa Tyr
           95
                               100
                                                   105
Thr Ala Lys Ala Xaa Leu Ala Gly Thr Leu Ser Leu Met Leu Ile Cys
                           115
                                               120
Thr Leu Leu Glu Phe Cys Xaa Xaa Val Leu Thr Ala Val Leu Arg Trp
                     130
                                           135
Lys Gln Ala Tyr Ser Asp Phe Pro Gly Ser Val Leu Phe Leu Pro Xaa
                                      150
Ser Tyr Ile Gly Asn Ser Gly Met Ser Ser Lys Met Thr His Asp Cys
               160
Gly Tyr Glu Glu Leu Leu Thr Ser
            175
```

Phe

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<210> 433
<211> 86
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -14..-1
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<400> 433 Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp Cys -5 -10 Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Leu Arg Ser Ser Ala 10 . 15 Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly Trp 20 25 Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg Leu 40 45 Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu Gly 55 60 His Arg Ile Cys Asp Leu 70

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<210> 434
<211> 144
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -58..-1
<400> 434
Met Thr Arg Leu Cys Leu Pro Arg Pro Glu Ala Arg Glu Asp Pro Ile
                              -50
Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser Pro
                          -35
Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu Leu
                      -20
                                        -15
Asp Ser Val Leu Trp Leu Gly Ala Leu Gly Leu Thr Ile Gln Ala Val
-10
                                     1
               -5
Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Leu Val Ser Phe Leu
        10
                             15
Thr Phe Asp Leu Leu His Arg Pro Ala Val Thr Leu Cys His Ser Ala
                                            35
                         30
Asn Phe Ser Pro Gly Ala Arg Val Arg Gly Pro Val Lys Val Leu Asp
                      45
Ser Arg Arg Leu Tyr Ser Cys Lys Trp Val Gln Ser Gln Asp Asn Leu
                  60
                                     65
Ala Ser Arg Lys His Cys Cys Cys Cys Ser Trp Gly Trp Ala Arg Ser
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<210> 435 <211> 121

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<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 435
Met Glu Arg Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala
                      -10
                               -5
Ser Ala Gly Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln
              5
                                 10
Cys Phe Lys Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser
   20
                              25
Pro Leu Asp Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Ser
                         40
Glu Ser Pro Pro Gly Arg Gly Xaa Val Pro Xaa Ala Gly Glu Xaa Pro
                     55
                               60
Val Pro Pro Pro Leu Xaa Asp Leu Xaa Met Thr Pro Arg Xaa Xaa Arg
                                  75
Ala Trp Gly Pro Val Gly Pro Lys Val Pro Pro Ala Val Ser Pro Ala
              85
Leu Gly Ser Gly Glu His Pro Xaa Xaa
           100
```

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<210> 436
<211> 162
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 436
Met Glu Arg Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala
            -10
Ser Ala Gly Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln
                                  10
Cys Phe Lys Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser
         20
                             25
Pro Leu Asp Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Lys
                          40
Trp Ser Val Arg Val Leu Leu Ser Lys Arg Cys Ala Pro Arg Cys Pro
                                        60
Asn Asp Asn Met Xaa Phe Glu Trp Ser Pro Ala Pro Met Val Gln Gly
                                      75
Val Ile Thr Arg Arg Cys Cys Ser Trp Ala Leu Cys Asn Arg Ala Leu
               85
                                  90
Thr Pro Gln Glu Gly Arg Trp Ala Leu Xaa Gly Gly Leu Leu Leu Gln
                             105
Asp Pro Ser Arg Gly Xaa Lys Thr Trp Val Arg Pro Gln Leu Gly Leu
                       120
                                             125
Pro Leu Cys Leu Pro Xaa Ser Asn Pro Leu Cys Pro Xaa Glu Thr Gln
           135
Glu Gly
145
```

<210> 437 <211> 110

```
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 437
Met Xaa Leu Met Val Leu Val Phe Thr Ile Gly Leu Thr Leu Leu Leu
                   -15
                                       -10
Gly Xaa Gln Ala Met Pro Ala Asn Arg Leu Ser Cys Tyr Arg Lys Ile
               1
Leu Lys Asp His Asn Cys His Asn Leu Pro Glu Gly Val Ala Asp Leu
       15
                            20
Thr Gln Ile Asp Val Asn Val Gln Asp His Phe Trp Asp Gly Lys Gly
                                           40
                       35
Cys Glu Met Ile Cys Tyr Cys Asn Phe Lys Arg Ile Ala Leu Leu Pro
45
                   50
                                        55
Lys Arg Arg Phe Leu Trp Thr Lys Asp Leu Phe Arg Asp Ser Leu Gln
                65
Gln Ser Met Arg Ile Phe Met Tyr Ser Gly Glu His His Ser
                                85
<210> 438
<211> 71
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
<400> 438
Met Lys Leu Leu Thr His Asn Leu Leu Ser Ser His Val Arg Gly Val
                  -10
                                       -5
Gly Ser Arg Gly Phe Pro Leu Arg Leu Gln Ala Thr Glu Val Arg Ile
                                10
Cys Pro Val Glu Phe Asn Pro Asn Phe Val Ala Arg Met Ile Pro Lys
                            25
                                                30
Val Glu Trp Ser Ala Phe Leu Glu Ala Xaa Asp Asn Leu Arg Leu Ile
                       40
Gln Val Pro Arg Arg Ala Gly
<210> 439
<211> 99
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1
<400> 439
Met Lys Ser Ala Lys Leu Gly Phe Leu Leu Arg Phe Phe Ile Phe Cys
                -20
                                    -15
```

<210> 440

```
      Ser
      Leu
      Asn
      Thr
      Leu
      Leu
      Leu
      Gly
      Gly
      Val
      Asn
      Lys
      Ile
      Ala
      Glu
      Lys

      Ile
      Cys
      Gly
      Asp
      Leu
      Lys
      Leu
      Asp
      Met
      Asn
      Phe
      Gly

      Ile
      Cys
      Gly
      Asp
      Leu
      Lys
      Lys
      Lys
      Asp
      Arg
      Thr
      Ser
      Lys
      Lys
      Asp
      A
```

```
<211> 169
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 440
Met Arg Lys Pro Ala Ala Gly Phe Leu Pro Ser Leu Leu Lys Val Leu
                   -20
                                      -15 -10
Leu Leu Pro Leu Ala Pro Ala Ala Ala Gln Asp Ser Thr Gln Ala Ser
Thr Pro Gly Ser Pro Leu Ser Pro Thr Glu Tyr Gln Arg Phe Phe Ala
Leu Leu Thr Pro Thr Trp Lys Ala Glu Thr Thr Cys Arg Leu Arg Ala
                       30
Thr His Gly Cys Arg Asn Pro Thr Leu Val Gln Leu Asp Gln Tyr Glu
                   45
                                       50
Asn His Gly Leu Val Pro Asp Gly Ala Val Cys Ser Asn Leu Pro Tyr
                                   65
Ala Ser Trp Phe Glu Ser Phe Cys Gln Phe Thr His Tyr Arg Cys Ser
           75
Asn His Val Tyr Tyr Ala Lys Arg Val Leu Cys Ser Gln Pro Val Ser
                          95
Ile Leu Ser Pro Asn Thr Leu Lys Glu Ile Glu Xaa Ser Ala Glu Val
                       110
                                         115
Ser Pro Thr Thr Asp Asp Leu Pro His Leu Thr Pro Leu His Ser Asp
                   125
                                      130
Arg Thr Pro Asp Leu Pro Ala Leu Ala
               140
```

Ala Asp Cys Gly Thr Ile Leu Leu Gln Asp Lys Gln Arg Lys Ile Tyr -55 -50 Cys Val Ala Cys Gln Glu Leu Asp Ser Asp Val Asp Lys Asp Asn Pro -35 -40 Ala Leu Asn Ala Gln Ala Ala Leu Ser Gln Ala Arg Glu His Gln Leu -20 -25 Ala Ser Ala Ser Glu Leu Pro Leu Gly Ser Arg Pro Ala Pro Gln Pro Pro Val Pro Arg Pro Glu His Cys Glu Gly Ala Ala Ala Gly Leu Lys 15 Ala Ala Gln Gly Pro Pro Ala Pro Ala Val Pro Pro Asn Thr Xaa Val 25 30 Met Ala Cys Thr Gln Thr Ala Leu Leu Gln Lys Leu Thr Trp Ala Ser 45 Ala Glu Leu Gly Ser Xaa Thr Ser Xaa Gly Lys Xaa Ala Ser Ser Cys 60 Val Ala Leu Ser Ala His Val Arg Arg Pro Cys Ala Ala Cys Ser Ser 75 Tyr Ser Thr Lys Arg Ser Pro

<210> 442 <211> 70 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1

<400> 442

 Met Ile Leu Cys
 Phe Leu Leu Pro His His Arg
 Leu Gln Glu Ala Arg

 -15
 -10
 -5
 1

 Gln Ile Gln Val Leu Lys
 Met Leu Pro Arg
 Glu Lys
 Leu Arg
 Arg

 Glu Glu Arg
 Lys
 Gln Ile Asn
 Gly Lys
 Lys
 Xaa
 Arg
 Thr Lys
 Tyr
 Glu Glu Arg

 Thr Pro Arg
 Lys
 Xaa Gly Lys
 Lys
 Gly Gly Asn
 Xaa Xaa Xaa Xaa
 Xaa Arg

 Xaa Leu Ser
 Lys
 Arg
 Asp

<210> 443 <211> 381 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -33..-1

```
Lys Met Ala Thr Val Lys Ser Glu Leu Ile Glu Arg Phe Thr Ser Glu
Lys Pro Val His His Ser Lys Val Ser Ile Ile Gly Thr Gly Ser Val
                               40
Gly Met Ala Cys Ala Ile Ser Ile Leu Leu Lys Gly Leu Ser Asp Glu
Leu Ala Leu Val Asp Leu Asp Glu Xaa Lys Leu Lys Gly Glu Thr Met
                   70
Asp Leu Gln His Gly Ser Pro Phe Thr Lys Met Pro Asn Ile Val Cys
                   85
                               90
Ser Lys Xaa Tyr Phe Val Thr Ala Asn Ser Asn Leu Val Ile Ile Thr
               100
                                 105
Ala Gly Ala Arg Gln Xaa Lys Gly Glu Thr Arg Leu Asn Leu Xaa Gln
                               120
Arg Asn Val Ala Ile Phe Lys Leu Met Ile Ser Ser Ile Val Gln Tyr
        130
                           135
Ser Pro His Cys Lys Leu Ile Ile Val Ser Asn Pro Val Asp Ile Leu
                      150
Thr Tyr Val Ala Trp Lys Leu Ser Ala Phe Pro Lys Asn Arg Ile Ile
                   165
                                       170
Gly Ser Gly Cys Asn Leu Ile Xaa Ala Arg Phe Arg Phe Leu Ile Gly
               180
                                   185
Gln Lys Leu Gly Ile His Ser Glu Ser Cys His Gly Trp Ile Leu Gly
                               200
Glu His Gly Asp Ser Ser Val Pro Val Trp Ser Gly Val Asn Ile Ala
                          215
Gly Val Pro Leu Lys Asp Leu Asn Ser Asp Ile Gly Thr Asp Lys Asp
                       230
                                          235
Pro Glu Gln Trp Lys Asn Val His Lys Glu Val Thr Ala Thr Ala Tyr
                   245
                                      250
Glu Ile Ile Lys Met Lys Gly Tyr Thr Ser Trp Ala Ile Gly Leu Ser
               260
                                   265
Val Ala Asp Leu Thr Glu Ser Ile Leu Lys Asn Leu Arg Arg Ile His
           275
                               280
Pro Val Ser Thr Ile Thr Lys Gly Leu Tyr Gly Ile Xaa Glu Glu Val
                          295
Phe Leu Ser Ile Pro Cys Ile Leu Gly Glu Asn Gly Ile Thr Asn Leu
                      310
                                         315
Ile Lys Ile Lys Leu Thr Pro Glu Glu Glu Ala His Leu Lys Lys Ser
                   325
                                      330
Ala Lys Thr Leu Trp Glu Ile Gln Asn Lys Leu Lys Leu
               340
```

```
<210> 445
<211> 50
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 445
Met Val Leu Thr Thr Leu Pro Leu Pro Ser Ala Asn Ser Pro Val Asn
                           -30
     -35
Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala Leu
                        -15
Ser Pro Cys Leu Thr Ala Pro Lys Ser Pro Arg Leu Ala Met Met Pro
                    1
                                    5
-5
Asp Asn
<210> 446
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 446
Met Thr Pro Trp Cys Leu Ala Cys Leu Gly Arg Arg Pro Leu Ala Ser
                        -20
                                            -15
Leu Gln Trp Ser Leu Thr Leu Ala Trp Cys Gly Ser Gly Ser His Trp
                   - 5
                                        1
Thr Glu Arg Pro Xaa Gln Xaa Ser Pro Trp Xaa Ser Leu Ser Ala Thr
                                15
            10
Thr Arg Gly
       25
<210> 447
<211> 242
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
<400> 447 -
Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val
-30
                 -25
                                        -20
Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Pro
                                     -5
                -10
Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu
        5
                            10
Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu
                        25
                                            30
Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly
```

40 45 Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly 55 60 Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Met Thr Asp Asn 70 75 Lys Thr Gly Glu Val Leu Ile Ser Glu Asn Val Val Ala Ser Ile Gln 90 Pro Xaa Glu Gly Xaa Phe Glu Gly Asp Leu Lys Val Pro Arg Met Glu 105 110 Glu Lys Glu Ala Leu Val Pro Xaa Gln Lys Ala Thr Asp Ser Phe His 120 125 Thr Glu Leu His Pro Arg Val Ala Phe Trp Ile Ile Lys Leu Pro Arg 135 140 Arg Arg Ser His Gln Asp Ala Leu Glu Gly Gly His Trp Leu Xaa Glu 150 155 Lys Arg His Arg Leu Gln Ala Ile Arg Asp Gly Leu Arg Lys Gly Thr 170 175 His Lys Asp Xaa Leu Xaa Xaa Gly Thr Glu Ser Ser His Ser Arg 185 190 Leu Ser Pro Arg Lys Xaa His Leu Leu Tyr Ile Leu Xaa Pro Ser Arg Gln Leu

<210> 448 <211> 154 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1

<400> 448

Met Gly Ser Lys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu -55 -50 Arg Gln Arg Arg Gln Lys Leu Leu Leu Ala Gln Leu His His Arg Lys -40 -35 Arg Val Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu -20 Val Arg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln -5 · Cys Trp Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln 10 15 Ala Leu Leu Gly Val Tyr Val Ile Gln Glu Gln Ala Ala Val Lys Leu 30 Gln Ser Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met 45 Cys Asn Ala Leu Cys Leu Phe Gln Val Pro Lys Ser Ser Leu Ala Phe 60

Gln Thr Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln
70 75 80

Pro Glu Phe His Ile Glu Ile Leu Ser Ile
85 90

<210> 449 <211> 89 <212> PRT <213> Homo sapiens

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<220> <221> SIGNAL <222> -61..-1 <400> 449 Met Asn Ala Ala Ile Asn Thr Gly Pro Ala Pro Ala Val Thr Lys Thr -55 - 50 Glu Thr Glu Val Gln Asn Pro Asp Val Leu Trp Asp Leu Asp Ile Pro -40 -35 -45 Glu Ala Arg Ser His Ala Asp Gln Asp Ser Asn Pro Lys Ala Glu Ala -25 -20 Leu Leu Pro Cys Asn Leu His Cys Ser Trp Leu His Ser Ser Pro Arg -10 -5 Pro Asp Pro His Ser His Phe Pro Ser Xaa Arg Arg Cys Pro Leu Pro 10 His Pro Cys Ala Thr Tyr Pro Pro Xaa 25 <210> 450 <211> 73 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -26..-1 <400> 450 Met Arg Met Ser Leu Ala Gln Arg Val Leu Thr Trp Leu Phe Thr -20 Leu Leu Phe Leu Ile Met Leu Val Leu Lys Leu Asp Glu Lys Ala Pro -5 1 Trp Asn Trp Phe Leu Ile Phe Ile Pro Val Trp Ile Phe Asp Thr Ile 10 . 20 15 Leu Leu Val Leu Leu Ile Val Lys Met Ala Gly Arg Cys Lys Ser Gly 25 30 Phe Asp Leu Asp Met Asp His Thr Ile 40 <210> 451 <211> 54 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -34..-1 <400> 451 Met Ile Pro Leu Ile Ser His Leu Ala Glu Ala Ala Pro Pro Thr Ser -30 -25 Trp Ser Leu Ile Ser Ser Val Leu Asn Val Gly His Leu Leu Phe Ser -10 -15 Ser Ala Cys Ser Val Ser Leu Glu Ala Leu Ser Thr Arg Asn Ile Lys 1

Ala Ile Ile Leu Met Lys

20

<210> 452

<210> 453

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<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -38..-1
<400> 452
Met Glu Ser Pro Gln Leu His Cys Ile Leu Asn Ser Asn Ser Val Ala
                               ~30
Cys Ser Phe Ala Val Gly Ala Gly Phe Leu Ala Phe Leu Ser Cys Leu
                           -15
                                              -10
Ala Phe Leu Val Leu Asp Thr Gln Glu Thr Arg Ile Ala Gly Thr Arg
                       1
Phe Lys Thr Ala Phe Gln Leu Leu Asp Phe Ile Leu Ala Val Leu Trp
               15
                                   20
Ala Val Val Trp Phe Met Gly Phe Cys Phe Leu Ala Asn Gln Trp Gln
           30
                               35
His Ser Pro Pro Lys Glu Xaa Leu Leu Gly Ser Ser Ser Ala Gln Ala
                           50
Ala Ile Gly Xaa His Leu Leu His Pro Cys Leu Asp Ile Pro Xaa
                       65
Leu Pro Gly Xaa Pro Gly Pro Pro Lys
```

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<211> 166
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 453
Met Ser Thr Val Gly Leu Phe His Phe Pro Thr Pro Leu Thr Arg Ile
                            -30
Cys Pro Ala Pro Trp Gly Leu Arg Leu Trp Glu Lys Leu Thr Leu Leu
                        -15
                                            -10
Ser Pro Gly Ile Ala Val Thr Pro Val Gln Met Ala Gly Lys Lys Asp
Tyr Pro Ala Leu Leu Ser Leu Asp Glu Asn Glu Leu Glu Glu Gln Phe
            15
                                20
Val Lys Gly His Gly Pro Gly Gly Gln Ala Thr Asn Lys Thr Ser Asn
                            35
Cys Val Val Leu Lys Xaa Ile Pro Ser Gly Ile Val Val Lys Cys His
                        50
                                            55
Gln Thr Arg Ser Val Asp Gln Asn Arg Lys Leu Ala Arg Lys Ile Leu
Gln Glu Lys Val Xaa Val Phe Tyr Asn Gly Glu Asn Ser Pro Val His
                                    85
Lys Glu Lys Arg Glu Ala Ala Lys Lys Gln Glu Arg Lys Lys Arg
                               100
                                                    105
Ala Lys Glu Thr Leu Glu Lys Lys Xaa Leu Leu Lys Xaa Leu Trp Glu
        110
                            115
```

-15

1

Ser Ser Lys Lys Val His 125

<210> 454 <211> 180 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -26..-1 <400> 454 Met Gly Ile Gln Thr Ser Pro Val Leu Leu Ala Ser Leu Gly Val Gly -25 -20 Leu Val Thr Leu Leu Gly Leu Ala Val Gly Ser Tyr Leu Val Arg Arg -5 Ser Arg Arg Pro Gln Val Thr Leu Leu Asp Pro Asn Glu Lys Tyr Leu 15 10 30 45

Leu Arg Leu Leu Asp Lys Thr Thr Val Ser His Asn Thr Lys Arg Phe 35 Arg Phe Ala Leu Pro Thr Ala His His Thr Leu Gly Leu Pro Val Gly 50 Lys His Ile Tyr Leu Ser Thr Arg Ile Asp Gly Ser Leu Val Ile Arg 60 65 Pro Tyr Thr Pro Val Thr Ser Asp Glu Asp Gln Gly Tyr Val Asp Leu 80 75 Val Xaa Lys Val Tyr Leu Lys Gly Val His Pro Lys Phe Pro Glu Gly 95 Gly Lys Met Ser Xaa Tyr Leu Asp Xaa Leu Lys Val Gly Asp Xaa Val 115

110 Glu Phe Xaa Gly Pro Ser Gly Leu Leu Thr Tyr Thr Gly Lys Gly His 125 . 130 Phe Asn Ile Gln Pro Asn Lys Asn Leu His Gln Asn Pro Glu Trp Arg 140 145

Arg Asn Trp Glu

<210> 455 <211> 91 <212> PRT <213> Homo sapiens

<220> <221> SIGNAL <222> -64..-1

<400> 455 Met Thr Pro Arg Ile Leu Ser Glu Val Gln Phe Ser Ala Phe Cys Pro -60 -55 Tyr Trp Thr Ile Ala Arg Ile Leu Glu Arg Val Gly Ser Ala Cys Phe -45 -40 Arg Leu Glu Leu Cys Ala Ala Ile Val Gly Tyr Phe Val Leu Asp Val -25 Arg Thr Phe Leu Phe Ile Val Val Cys Val Ile Cys Val Thr Leu Asn -10 -5 Phe Pro Arg Phe Tyr Phe Leu Cys Leu Ser Ser Leu Thr Ala Phe Gly 10 Thr Pro Pro Ile Gly Val His Ile Pro Ser Pro

20

```
25
```

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<210> 456
<211> 257
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 456
Met Arg Arg Ile Ser Leu Thr Ser Ser Pro Val Arg Leu Leu Leu Xaa
           -20
                    -15
Leu Leu Leu Leu Ile Ala Leu Glu Ile Met Val Gly Gly His Ser
                           1
Leu Cys Phe Asn Phe Thr Ile Lys Ser Leu Ser Arg Pro Gly Gln Pro
                   15
                                       20
Trp Cys Glu Ala His Val Phe Leu Asn Lys Asn Leu Phe Leu Gln Tyr
               30
                                  35
Asn Ser Asp Asn Asn Met Val Lys Pro Leu Gly Leu Leu Gly Lys Lys
                              50
Val Tyr Ala Thr Ser Thr Trp Gly Glu Leu Thr Gln Thr Leu Gly Glu
                          65
Val Gly Arg Asp Leu Arg Met Leu Leu Cys Asp Ile Lys Pro Gln Ile
                      80
                                         85
Lys Thr Ser Asp Pro Ser Thr Leu Gln Val Xaa Xaa Phe Cys Gln Arg
                  95
                                      100
Glu Ala Glu Arg Cys Thr Gly Ala Ser Trp Gln Phe Ala Thr Asn Gly
               110
                                   115
Glu Lys Ser Leu Leu Phe Asp Ala Met Asn Met Thr Trp Thr Val Ile
          125
                               130
                                                  135
Asn His Glu Ala Ser Xaa Ile Lys Glu Thr Trp Lys Lys Asp Arg Xaa
                          145
                                              150
Leu Glu Xaa Tyr Phe Arg Lys Leu Ser Lys Gly Asp Cys Asp His Trp
                      160
                                         165
Leu Arg Glu Phe Leu Gly His Trp Glu Ala Met Pro Xaa Pro Xaa Val
                  175
                                     180
Ser Pro Xaa Asn Ala Ser Xaa Ile His Trp Ser Ser Ser Xaa Leu Pro
              190
                                  195
Xaa Xaa Trp Ile Ile Leu Gly Ala Phe Ile Leu Leu Xaa Leu Met Gly
                              210
Ile Val Leu Ile Cys Val Trp Trp Gln Asn Gly Xaa Xaa Ser Thr Xaa
                           225
Xaa
```

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<210> 457
<211> 193
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -60..-1
```

<400> 457

Met Cys Pro Ser Leu Glu Glu Ala Pro Ser Val Lys Gly Thr Leu Pro
-60 -55 -50 -45

Cys Ser Gly Gln Gln Gln Pro Phe Pro Phe Gly Ala Ser Asn Ile Pro -40 -35 Leu Leu Cly Arg Ser Arg Lys Val Ala Arg Gly Ala Pro Val Leu -20 Trp Pro Phe Leu Thr Trp Ile Asn Pro Ala Leu Ser Ile Cys Asp Pro Leu Gly Ser Cys Gly Trp Xaa Cys His Thr Ala Gln Val Pro Ala Pro 10 Leu Gln Leu Pro Thr Ala Cys Pro Pro Leu Pro His Gly Thr Arg Ala 25 30 Val Gly Pro Thr Pro Gly Leu Pro Glu Ala Ala Pro Xaa Thr 45 Xaa Gly Ala Leu Ser Ser Arg Ser Arg His Trp Ser Cys Ser Ile Val 60 Xaa Cys Leu His Leu His Xaa Leu Leu Ser Val Glu Thr Arg Xaa Phe Xaa Lys His Leu Leu Val Leu Leu Val Ala Val Ala His Ser Val Leu 95 Glu Pro Pro Ala Leu Val Pro Asn Val Gln Cys Glu Met Cys Thr His 105 110 Ser Gly Pro Arg Asp Leu Glu Ala Ala Val Val Ser Pro Ala Pro Trp 125 Glu

<210> 458 <211> 107 <212> PRT <213> Homo sapiens

<220>
<221> SIGNAL
<222> -28..-1

-400× 458

Met Val Leu Thr Leu Gly Glu Ser Trp Pro Val Leu Val Gly Arg Arg -25 -20 Phe Leu Ser Leu Ser Ala Ala Asp Gly Ser Asp Gly Ser His Asp Ser -10 -5 Trp Asp Val Glu Arg Val Ala Glu Trp Pro Trp Leu Ser Gly Thr Ile 10 15 Arg Ala Val Ser His Thr Asp Val Thr Lys Lys Asp Leu Lys Val Cys 30 25 Val Glu Phe Xaa Gly Glu Ser Trp Arg Lys Arg Arg Trp Ile Glu Val 45 Tyr Ser Leu Leu Arg Lys Ala Phe Leu Val Lys His Asn Leu Val Leu 60

Ala Glu Arg Lys Ser Pro Glu Ile Ser Trp Gly

<210> 459
<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -13..-1

<400> 459 Met Leu Val Leu Arg Ser Ala Leu Thr Arg Ala Leu Ala Ser Arg Thr -10 -5 Leu Ala Pro Gln Met Cys Ser Ser Phe Ala Thr Gly Pro Arg Gln Tyr 10 15 Asp Gly Ile Phe Tyr Glu Phe Arg Ser Tyr Tyr Leu Lys Pro Ser Lys 25 30 Met Asn Glu Phe Leu Glu Asn Phe Glu Lys Asn Ala Gln Leu Arg Thr 40 45 Ala His Ser Glu Leu Val Gly Tyr Trp Ser Val Xaa Phe Gly Gly Arg 60 Met Xaa Thr Val Phe His Ile Trp Lys Tyr Asp Asn Phe Ala His Arg 75 Thr Glu Phe Gln Lys Ala Leu Ala Lys Asp Lys Glu Trp Gln Glu Gln 90 Phe Leu Ile Pro Asn Leu Ala Leu Asn 100

<210> 460 <211> 44 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -17..-1 <400> 460 Met Lys Val Gly Val Leu Trp Leu Ile Ser Phe Phe Thr Phe Thr Asp -15 -10 -5 Gly His Gly Gly Phe Leu Gly Val Ser Trp Cys Tyr Val Ser Tyr Leu 5 10 Phe Ser Thr Asn Ser Pro Leu Ser Phe Arg Arg Ile

20

70

<210> 461 <211> 109 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1 <400> 461 Met Cys Leu Leu Thr Ala Leu Val Thr Gln Val Ile Ser Leu Arg Lys -10 -5 Asn Ala Glu Arg Thr Cys Leu Cys Lys Arg Arg Trp Pro Trp Xaa Pro 10 15 Ser Pro Arg Ile Tyr Cys Ser Ser Thr Pro Cys Asp Ser Lys Phe Pro 25 30 Thr Val Tyr Ser Ser Ala Pro Phe His Ala Pro Leu Pro Val Gln Asn 45 Ser Leu Trp Gly His Pro Leu His Gly Cys Ser Trp Gln Cys His His

60

Pro Gln Gly Gln Asn Leu Gln Pro Ala Ser Leu Xaa Thr His Leu Ser

75

Lys Pro Lys Arg His Phe Xaa Lys Lys Xaa Cys Gln Ala

85

90

95

<210> 462 <211> 143 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -41..-1

<400> 462

Met Ala Thr Ala Thr Glu Gln Trp Val Leu Val Glu Met Val Gln Ala -35 -30 Leu Tyr Glu Ala Pro Ala Tyr His Leu Ile Leu Glu Gly Ile Leu Ile -20 -15 Leu Trp Ile Ile Arg Leu Leu Phe Ser Lys Thr Tyr Lys Leu Gln Glu -5 1 Arg Ser Asp Leu Thr Val Lys Glu Lys Glu Glu Leu Ile Glu Glu Trp 10 15 20 Gln Pro Glu Pro Leu Val Pro Pro Val Pro Lys Asp His Pro Ala Leu 30 35 Asn Tyr Asn Ile Val Ser Gly Pro Pro Ser His Lys Thr Val Val Asn 45 50 Gly Lys Glu Cys Ile Asn Phe Ala Ser Phe Asn Phe Leu Gly Leu Leu 60 65 Asp Asn Pro Arg Val Lys Ala Ala Leu Ala Ser Leu Lys Lys Tyr 80 Gly Val Gly Thr Cys Gly Pro Cys Gly Phe Tyr Gly Thr Phe Glu 95

<210> 463 <211> 232 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -30..-1

Met Ala Ala Thr Ser Gly Thr Asp Glu Pro Val Ser Gly Glu Leu Val -25 -20 Ser Val Ala His Ala Leu Ser Leu Pro Ala Glu Ser Tyr Gly Asn Xaa -10 -5 Xaa Asp Ile Glu Met Ala Trp Ala Met Arg Ala Met Gln His Ala Glu 10 , 15 Val Tyr Tyr Lys Leu Ile Ser Ser Val Asp Pro Gln Phe Leu Lys Leu 25 30 Thr Lys Val Asp Asp Gln Ile Tyr Ser Glu Phe Arg Lys Asn Phe Glu 40 45 Thr Leu Arg Ile Asp Val Leu Xaa Pro Glu Xaa Leu Lys Ser Glu Ser 55 60 Ala Lys Glu Pro Pro Gly Tyr Asn Ser Leu Pro Leu Lys Leu Leu Gly 75 Thr Gly Lys Ala Ile Thr Lys Leu Phe Ile Ser Val Phe Arg Thr Lys 90 95 Lys Glu Arg Lys Glu Ser Thr Met Glu Glu Lys Lys Glu Leu Thr Val

```
105
                                         110
Glu Lys Lys Arg Thr Pro Arg Met Glu Glu Arg Lys Glu Leu Ile Val
                 120
                                     125
Glu Lys Lys Lys Arg Lys Glu Ser Thr Glu Lys Thr Lys Leu Thr Lys
              135
                                 140
Glu Glu Lys Lys Gly Lys Lys Leu Thr Lys Lys Ser Thr Lys Val Val
          150
                    155
                                        160
Lys Lys Leu Cys Lys Val Tyr Arg Glu Gln His Ser Arg Ser Tyr Asp
                         170
                                   175
Ser Ile Glu Thr Thr Ser Thr Thr Val Leu Leu Ala Gln Thr Pro Leu
                      185
Val Lys Cys Lys Phe Leu Tyr Asn
<210> 464
<211> 61
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 464
Met Thr Phe Arg His Gln Asp Asn Ser Leu Met Phe Phe Ser Met Met
                      -15
                                         -10
Ala Thr Cys Thr Ser Asn Val Gly Phe Thr His Thr Thr Met Asn Cys
                   1
                                5
Ser Leu Thr Ser Pro Val Asp Phe Lys Asp Leu Leu Arg Val Leu Leu
          15
                           20
Ile Lys Phe Gly Tyr Asp Arg Lys Ser Thr Ile Lys Ser
                          35
<210> 465
<211> 34
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 465
Met Phe Leu Lys Ser Gly Ala Gly Leu Ser Ser Cys Leu Leu Pro Leu
               -15
                               -10
Cys Trp Leu Glu Arg Lys Asp His Gly Arg Arg Pro Ser Xaa His Pro
                          5
Gly Arg
    15
```

<210> 466 <211> 215 <212> PRT <213> Homo sapiens

<220>

```
<221> SIGNAL <222> -54..-1
```

<400> 466

Met Asn Xaa Tyr Ala Ser Pro Phe Asn Xaa Gln Leu Xaa Tyr Leu Xaa -50 -45 -40

Leu Ser Arg Phe Glu Cys Val His Arg Asp Gly Arg Val Ile Thr Leu
-35 -30 -25

Ser Tyr Gln Glu Gln Glu Leu Gln Asp Phe Leu Leu Ser Gln Met Ser -20 -15 -10

Gln His Gln Val His Ala Val Gln Gln Leu Ala Lys Val Met Gly Trp
-5 1 5 10

Gln Val Leu Ser Phe Ser Asn His Val Gly Leu Gly Pro Ile Glu Ser 15 20 25

Xaa Gly Asn Ala Ser Ala Ile Thr Val Ala Pro Gln Val Val Thr Met 30 35 40

Leu Phe Gln Phe Val Met Asp Leu Lys Val Ala Ala Arg Leu Trp Phe
45 50 55

Ser Phe Leu Val Thr Asn Val Lys Thr Phe Gln Lys Val Met Phe Tyr 60 65 70

Lys Ile Thr Asn Gly Val Ile Phe Val Gly His Ser Lys Lys Phe Ser 75 80 85 90

Gly Ile Lys Trp Lys Val Xaa Ile Leu Phe Ile Lys Trp Xaa Cys Leu
95 100 105

Cys Leu His Leu Ala Leu Val Tyr Tyr Asp Phe Phe Gln Met Phe Pro 110 115 120

Lys Xaa Val Ser Xaa Asn Phe Asp Leu Lys Cys Leu Gln Ile Asn Tyr
125
130
135

Lys His Lys Glu Glu Ile Thr Ser Lys Arg Val Leu Phe Leu Lys Ile 140 145 150

Ile Ile Arg Lys Cys Phe Ile

<210> 467

<211> 27

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -17..-1

<400> 467

Met Val Val His Leu Leu Tyr Ala His Leu Ser Phe Thr Ser Lys Arg
-15 -10 -5

Ala Val Val Met Leu Lys Leu Glu Ile Thr Phe 1 5 10

<210> 468

<211> 85

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -24..-1

<400> 468

 Met
 Cys
 Ser
 His
 Ala
 Ser
 Met
 Ser
 Phe
 His
 Thr
 Leu
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<210> 469 <211> 51 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1

<210> 470 <211> 67 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -43..-1

<210> 471 <211> 63 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -71..-1

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<220>
<221> SIGNAL
<222> -15..-1
<400> 471
Met Gly Ile Leu Ser Thr Val Thr Ala Leu Thr Phe Ala Arg Ala Leu
                   -10
                                -5
Asp Gly Cys Arg Asn Gly Ile Ala His Pro Ala Ser Glu Lys His Arg
                               10
Leu Glu Lys Cys Arg Glu Leu Glu Ser Ser His Ser Ala Pro Gly Ser
                         25
       20
Thr Gln His Arg Arg Lys Thr Thr Arg Arg Asn Tyr Ser Ser Ala
                       40
<210> 472
<211> 179
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -58..-1
<400> 472
Met Ser Thr Gly Gln Leu Tyr Arg Met Glu Asp Ile Gly Arg Phe His
                               -50
Ser Gln Gln Pro Gly Ser Leu Thr Pro Ser Ser Pro Thr Val Gly Glu
                           -35
                                               -30
Ile Ile Tyr Asn Asn Thr Arg Asn Thr Leu Gly Trp Ile Gly Gly Ile
   -25
                       -20
                                           -15
Leu Met Gly Ser Phe Gln Gly Thr Ile Ala Gly Gln Gly Thr Gly Ala
                   -5
                                       1
Thr Ser Ile Ser Glu Leu Cys Lys Gly Gln Glu Leu Glu Pro Ser Gly
          10
                               15
Ala Gly Leu Thr Val Ala Pro Pro Gln Ala Val Ser Leu Gln Gly Ile
                           30
Tyr Thr Leu Pro Trp Leu Leu Gln Leu Phe His Ser Thr Ala Leu Xaa
                        45
Xaa Xaa Gln Gln Pro Asn Gly Ser Leu Ser Leu Asn Ile Ser Ser Ser
                   60
                                       65
His Ala Pro Xaa Pro Xaa Thr Cys Thr Leu Glu Pro Gly Val Asp Pro
              75
                                   80
Thr Arg Xaa Val Cys Ile Asn Pro His Pro Pro Pro Pro Ile Leu Lys
                               95
Xaa Pro Leu Ser Pro Tyr Pro Lys Pro Gln Leu Gly Thr His Ala Gly
                           110
Gln Val Asn
    120
<210> 473
<211> 238
<212> PRT
<213> Homo sapiens
<220>
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<400> 473
Met Xaa Xaa Phe Thr Asp Pro Ser Ser Val Asn Glu Lys Lys Arg Arg
           -65
Glu Arg Glu Glu Arg Gln Asn Ile Val Leu Trp Arg Gln Pro Leu Ile
-55
                   -50
Thr Leu Gln Tyr Phe Ser Leu Glu Ile Leu Val Ile Leu Lys Glu Trp
               -35
                               -30
Thr Ser Lys Leu Trp His Arg Gln Ser Ile Val Val Ser Phe Leu Leu
                              -15
Leu Leu Ala Gly Leu Ile Ala Thr Tyr Tyr Val Glu Gly Val His Gln
Gln Tyr Val Gln Arg Ile Glu Lys Gln Phe Leu Leu Tyr Ala Tyr Trp
                   15
Ile Gly Leu Gly Ile Leu Ser Ser Val Gly Leu Gly Thr Gly Leu His
               30
                                  35
Thr Phe Leu Leu Tyr Leu Gly Pro His Ile Ala Ser Val Thr Leu Ala
                               50
Ala Tyr Glu Cys Asn Ser Val Asn Phe Pro Glu Pro Pro Tyr Pro Asp
                          65
Gln Ile Ile Cys Pro Asp Glu Glu Gly Thr Glu Gly Thr Ile Ser Leu
                       80
                                          85
Trp Ser Ile Ile Ser Lys Val Arg Ile Glu Ala Cys Met Trp Gly Ile
                   95
                                       100
Gly Thr Ala Ile Gly Glu Leu Pro Pro Tyr Phe Met Ala Arg Ala Ala
              110
                                  115
Arg Leu Ser Gly Ala Glu Pro Asp Asp Glu Glu Tyr Gln Glu Phe Glu
          125
                              130
                                                 135
Glu Met Leu Glu His Ala Glu Ser Ala Gln Val Arg Thr Val Gly Ile
       140
                         145
                                              150
Glu Asn Arg Thr Leu Tyr Phe Phe Leu Lys Arg Leu Leu Arg
                       160
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<210> 474 <211> 178 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -37..-1

<400> 474

Met Glu Arg Gln Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln Phe -30 -25 Gln His Gln Gly Ala Val Glu Leu Leu Val Phe Asn Phe Leu Leu Ile -20 -15 Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg Phe Arg Phe 1 5 Leu His Glu Thr Gly Gly Ala Met Val Tyr Gly Leu Xaa Met Gly Leu 15 20 Ile Leu Xaa Tyr Ala Thr Ala Pro Thr Asp Ile Glu Ser Gly Xaa Val 35 Tyr Asp Cys Val Lys Leu Thr Phe Ser Pro Ser Thr Leu Leu Val Asn 50 55 Ile Thr Asp Gln Val Tyr Glu Tyr Lys Tyr Lys Arg Glu Ile Ser Gln 65 70 His Xaa Ile Asn Pro His Xaa Gly Asn Ala Ile Leu Glu Lys Met Thr 80 85 Phe Asp Pro Xaa Ile Phe Phe Asn Val Leu Leu Pro Pro Ile Ile Phe

```
100
His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly .
                   115
                                      120
   110
Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val
                      130
 125
Ile Gly
140
<210> 475
<211> 96
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 475
Met Ser Met Gln Phe Leu Phe Lys Met Val Ala Leu Cys Cys Leu
                       -15
                                         -10
Trp Lys Ile Ser Gly Cys Glu Glu Val Pro Leu Thr Tyr Asn Leu Leu
-5
                   1
Lys Cys Leu Leu Asp Lys Ala His Cys Val Leu Leu Thr Pro Cys Gly
                           20
           15
Tyr Ile Phe Ser Leu Ile Ser Pro Glu Ile Leu Lys Leu Thr Leu Ile
       30
                          35
Thr Leu Xaa Ile Leu Leu Ile Leu Lys Asn Leu His Leu Leu Trp Leu
Thr Val Ser Ser Xaa Cys Val His Arg Ser Ser Ala Arg Lys Glu Lys
<210> 476
<211> 41
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1
<400> 476
Met His Thr Phe Ala Asn Asp Arg Gly Leu Tyr Arg Ile Leu Leu Leu
            -20
                                -15
His Phe Tyr Cys Leu Leu Arg Ser Ser Glu Tyr Ile Leu Gly Tyr Lys
           - 5
                           1
Val Leu Gly Val Phe Phe Pro Ile Leu
   10
<210> 477
<211> 113
<212> PRT
<213> Homo sapiens
<220>
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<221> SIGNAL <222> -27..-1

<400> 477 Met Arg Xaa Lys Trp Lys Met Gly Gly Met Lys Tyr Ile Phe Ser Leu -20 Leu Phe Phe Leu Leu Glu Gly Gly Xaa Thr Glu Gln Val Xaa His Ser Glu Thr Tyr Cys Met Phe Gln Asp Lys Lys Tyr Arg Val Gly Glu 10 15 Arg Trp His Pro Tyr Leu Glu Pro Tyr Gly Leu Val Tyr Cys Val Asn 30 Cys Ile Cys Ser Glu Asn Gly Asn Val Leu Cys Ser Arg Val Arg Cys 4.5 Pro Asn Val His Cys Leu Ser Pro Val His Ile Pro His Leu Cys Cys 60 65 Pro Arg Cys Pro Glu Asp Ser Leu Pro Pro Val Asn Asn Xaa Val Thr Ser

<210> 478 <211> 250 <212> PRT <213> Homo sapiens

225

<221> SIGNAL <222> -18..-1

<400> 478

Met Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val -10 Gly Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Pro His Ser 10 Gln Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly 20 25 Ala Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu 40 Lys Pro Arg Tyr Ile Xaa His Leu Gly Gln His Asn Leu Gln Lys Glu 55 Glu Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro 70 Gly Phe Asn Asn Ser Leu Pro Asn Lys Asp Xaa Xaa Asn Asp Ile Met 85 90 Leu Val Xaa Met Xaa Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro 100 105 Leu Thr Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Leu Ile 115 120 Ser Gly Trp Gly Ser Thr Ser Ser Pro Gln Leu Arg Leu Pro His Thr 130 135 Leu Arg Cys Ala Asn Ile Thr Ile Ile Glu His Gln Lys Cys Glu Asn 145 150 155 Ala Tyr Pro Gly Asn Ile Thr Asp Thr Met Val Cys Ala Ser Val Gln 165 170 Glu Gly Gly Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val 180 185 Cys Asn Gln Ser Leu Gln Gly Ile Ile Ser Trp Gly Gln Asp Pro Cys 200 Ala Ile Thr Arg Lys Pro Gly Val Tyr Thr Lys Val Cys Lys Tyr Val 210 215 Asp Trp Ile Gln Glu Thr Met Lys Asn Asn

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<210> 479
<211> 151
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 479
Met Ala Ala Ser Thr Ser Met Val Pro Val Ala Val Thr Ala Ala Val
                                           -10
                       -15
Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile
                                   5
                   ı
Lys Lys Gln Leu Leu Leu Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu
           15
                               20
Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala
                           35
                                               40
Leu Pro Leu Ala Glu Leu Gln Pro Pro Pro Pro Ile Thr Glu Glu Asp
                                           55
                       50
Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val
                                       70
                   65
Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys Asn Ala Arg
               80
                                   85
Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val Arg Ala Ile
                               100
Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe Arg Thr Asn
                           115
Gly Lys Val Lys Ser Phe Lys
   125
<210> 480
<211> 239
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -25..-1
<400> 480
Met Pro Arg Lys Arg Lys Cys Asp Leu Arg Ala Val Arg Val Gly Leu
                                      -15
                   -20
Leu Leu Gly Gly Gly Val Tyr Gly Ser Arg Phe Arg Phe Thr Phe
                                  1
Pro Gly Cys Arg Ala Leu Ser Pro Trp Arg Val Arg Xaa Gln Arg Arg
                           15
                                               20
       10
Arg Cys Glu Met Ser Thr Met Phe Ala Asp Thr Leu Leu Ile Val Phe
                        30
                                           35
Ile Ser Val Cys Thr Ala Leu Leu Ala Glu Gly Ile Thr Trp Val Leu
                   45
Val Tyr Arg Thr Asp Lys Tyr Lys Arg Leu Lys Ala Glu Val Glu Lys
                                    65
Gln Ser Lys Lys Leu Glu Lys Lys Lys Glu Thr Ile Thr Glu Ser Ala
                               80
            75
```

Gly Arg Gln Cln Lys Lys Lys Ile Glu Arg Xaa Xaa Xaa Xaa Leu Xaa
90 95 100

Asn Asn Asn Arg Asp Leu Ser Met. Val Arg Met Lys Ser Met Phe Ala 105 110 115 Ile Gly Phe Cys Phe Thr Ala Leu Met Gly Met Phe Asn Ser Ile Phe 125 130 Asp Gly Arg Val Val Ala Lys Leu Pro Phe Thr Pro Leu Ser Xaa Xaa 140 145 Xaa Gly Leu Ser His Arg Asn Leu Leu Gly Asp Asp Thr Thr Asp Cys 160 Ser Phe Ile Phe Leu Xaa Ile Leu Cys Thr Met Ser Ile Arg Gln Asn 170 175 Ile Gln Lys Ile Leu Gly Leu Ala Pro Ser Arg Ala Ala Thr Lys Gln 185 190 195 Ala Gly Gly Phe Leu Gly Pro Pro Pro Pro Ser Gly Lys Phe Ser

<210> 481 <211> 208 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -92..-1

<400> 481 Met Arg Glu Pro Gln Lys Arg Thr Ala Thr Ile Ala Lys Xaa Xaa Ala -85 Xaa Glu Gly Leu Arg Asp Pro Tyr Gly Arg Leu Cys Gly Ser Glu His -70 -65 Pro Arg Arg Pro Pro Glu Arg Pro Glu Glu Asp Pro Ser Thr Pro Glu -55 -50 Glu Ala Ser Thr Thr Pro Glu Glu Ala Ser Ser Thr Ala Gln Ala Gln -40 -35 Lys Pro Ser Val Pro Arg Ser Asn Phe Gln Gly Thr Lys Lys Ser Leu -20 Leu Met Ser Ile Leu Ala Leu Ile Phe Ile Met Gly Asn Ser Ala Lys -10 -5 Glu Ala Leu Val Trp Lys Val Leu Gly Lys Leu Gly Met Gln Pro Gly 10 15 Arg Xaa His Ser Ile Phe Gly Asp Pro Lys Lys Ile Val Thr Glu Xaa 25 30 Phe Val Arg Arg Gly Tyr Leu Ile Tyr Xaa Pro Val Pro Arg Xaa Ser 45 Pro Val Glu Tyr Xaa Phe Phe Trp Gly Pro Arg Ala His Val Glu Ser 60 Ser Xaa Leu Lys Xaa Xaa His Phe Val Ala Arg Val Arg Asn Arg Cys 75 Ser Lys Asp Trp Pro Cys Asn Tyr Asp Trp Asp Ser Asp Asp Asp Ala 90 95 Glu Val Glu Ala Ile Leu Asn Ser Gly Ala Xaa Gly Tyr Ser Ala Pro

<210> 482 <211> 86 <212> PRT <213> Homo sapiens

<220>

<221> SIGNAL <222> -39..-1

<400> 482

Met Asn Val Gly Thr Ala His Xaa Xaa Val Asn Pro Asn Thr Arg Val
-35 -30 -25

Control of the Contro

Met Asn Ser Arg Gly Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly Leu
-20 -15 -10

Leu His Ile Val Leu Leu Ser Ile Pro Phe Val Ser Val Pro Val Val -5 1 5

Trp Thr Leu Thr Asn Leu Ile His Asn Met Gly Met Tyr Ile Phe Leu

10 15 20 25

His Thr Val Lys Gly Thr Pro Phe Gly Thr Pro Asp Gln Gly Lys Ala

His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys Ala 30 35 40

Arg Leu Leu Thr His Trp
45

<210> 483

<211> 40

<212> PRT

<213> Homo sapiens

<220'>

<221> SIGNAL

<222> -27..-1

<400> 483

Met Arg Thr Leu Phe Gly Ala Val Arg Ala Pro Phe Ser Ser Leu Thr
-25 -20 -15

Leu Leu Leu Ile Thr Pro Ser Pro Ser Pro Leu Leu Phe Asp Arg Gly
-10 -5 1 5

Leu Ser Leu Arg Ser Ala Met Ser

10

<210> 484

<211> 65

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -16..-1

<400> 484

Met Leu Gly Phe Phe Leu Phe Leu Ser Phe Val Leu Met Tyr Asp Gly
-15
-10
-5
Leu Arg Leu Phe Gly Ile Leu Ser Thr Cys Arg Val His His Thr Met

1 10 10 10 In the Levy Lie Agn Lie Cor Ser Phe Thr Ser Arg Val Lys Ly

Asn Gln Phe Leu Ile Asp Ile Ser Ser Phe Thr Ser Arg Val Lys Lys 20 25 30 Lys Ile Phe Leu Phe Tyr Ala Phe Xaa Gly Cys Xaa Phe Gln Ser Ala

35 40 45

Thr

<210> 485

<211> 130

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<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -55..-1

<400> 485

Met Ala Met Trp Asn Arg Pro Xaa Xaa Xaa Leu Pro Gln Gln Pro Leu
-55 -45 -46

-343-

Xaa Ala Glu Pro Thr Ala Glu Gly Glu Pro His Leu Pro Thr Gly Arg
-35 -30 -25

Xaa Xaa Thr Glu Ala Asn Arg Phe Ala Tyr Ala Ala Leu Cys Gly Ile
-20 -15 -10

Ser Leu Ser Gln Leu Phe Pro Glu Pro Glu His Ser Ser Phe Cys Thr
-5 1 5

Glu Phe Met Ala Gly Leu Val Xaa Trp Leu Glu Leu Ser Glu Ala Val 10 15 20 25

Leu Pro Thr Met Thr Ala Phe Ala Ser Gly Leu Gly Gly Glu Gly Xaa 30 35 40

Xaa Cys Val Cys Ser Asn Phe Thr Glu Gly Pro His Leu Glu Gly Arg
45 50 55

Pro Asp Gly Asp His Ser Gly Pro Ser Glu Leu Leu Thr Gln Gly Trp
60 65 70

Ala Leu 75

<210> 486

<211> 209

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -84..-1

<400> 486

Met Val Asn Phe Pro Gln Lys Ile Ala Gly Glu Leu Tyr Gly Pro Leu
-80 -75 -70

Met Leu Val Phe Thr Leu Val Ala Ile Leu Leu His Gly Met Lys Thr
-65 -60 -55

Ser Asp Thr Ile Ile Arg Glu Gly Thr Leu Met Gly Thr Ala Ile Gly
-50 -45 -40

Thr Cys Phe Gly Tyr Trp Leu Gly Val Ser Ser Phe Ile Tyr Phe Leu
-35
-25

Ala Tyr Leu Cys Asn Ala Gln Ile Thr Met Leu Gln Met Leu Ala Leu -20 -15 -10 -5

Leu Gly Tyr Gly Leu Phe Gly His Cys Ile Val Leu Phe Ile Thr Tyr

1 5 10

Asn Ile His Leu Arg Ala Leu Phe Tyr Leu Phe Trp Leu Leu Val Gly
15 20 25

Gly Leu Ser Thr Leu Arg Met Val Ala Val Leu Val Ser Arg Thr Val

Gly Pro Thr Xaa Arg Xaa Leu Leu Cys Gly Thr Leu Ala Ala Leu His 50 55 60

Met Leu Phe Leu Leu Tyr Leu His Phe Ala Tyr His Lys Xaa Val Xaa 65 70 75

Gly Ile Leu Asp Thr Leu Glu Gly Pro Asn Ile Pro Pro Ile Gln Arg 80 85 90

Val Pro Arg Asp Ile Pro Ala Met Leu Pro Ala Ala Arg Leu Pro Thr

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100
Thr Val Leu Asn Ala Thr Ala Lys Ala Val Ala Val Thr Leu Gln Ser
125
<210> 487
<211> 36
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
<400> 487
Met Gly Trp Gln Arg Trp Trp Cys Phe His Leu Gln Ala Glu Ala Ser
   -15 -10
Ala His Pro Pro Gln Gly Leu Gln Ala Gln Phe Ser Cys Cys Pro Trp
                  5
Val Gly Ile Cys
<210> 488
<211> 44
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -29..-1
<400> 488
Met Met Ser Ser Glu Leu Arg Arg Asn Pro His Phe Leu Lys Ser Asn
              -25 -20
Leu Phe Leu Gln Leu Leu Val Ser His Glu Ile Val Cys Ala Thr Glu
          -10 -5
Thr Val Thr Thr Asn Phe Leu Arg His Glu Lys Ala
   5
<210> 489
<211> 163
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -52..-1
<400> 489
Met Glu His Tyr Arg Lys Ala Gly Ser Val Glu Leu Pro Ala Pro Ser
              -45
     -50
Pro Met Pro Gln Leu Pro Pro Asp Thr Leu Glu Met Arg Val Arg Asp
              -30
                                        -25
Gly Ser Lys Ile Arg Asn Leu Leu Gly Leu Ala Leu Gly Arg Leu Glu
                                    -10
```

Gly Gly Ser Ala Arg His Val Val Phe Ser Gly Ser Gly Arg Ala Ala

```
Gly Lys Ala Val Ser Cys Ala Glu Ile Val Lys Arg Arg Val Pro Gly
                           20
Leu His Gln Leu Thr Lys Leu Xaa Phe Leu Gln Thr Glu Asp Ser Trp
                       35
Val Pro Xaa Ser Pro Asp Thr Gly Leu Xaa Pro Leu Thr Val Arg Arg
                   50
                                       55
His Val Pro Ala Xaa Trp Val Leu Leu Xaa Arg Asp Pro Leu Asp Pro
                                   70
Asn Glu Cys Gly Tyr Gln Pro Pro Gly Ala Pro Pro Gly Leu Gly Ser
           80
                             85
Met Pro Ser Ser Cys Gly Pro Arg Ser Xaa Lys Arg Ala Xaa Xaa
                           100
       95
Thr Arg Ser
   110
```

attannen et etakonin tartantakoa idenakoarran erroren etakon mentenakoarran erroren barran erroren barran erro

<210> 490 <211> 64 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -47..-1

<400> 490

<210> 491 <211> 218 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -50. -1

Met His His Gly Leu Thr Pro Leu Leu Gly Val His Glu Gln Lys -45 -40 Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala -30 -25 Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly -15 -10 -5 Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser 5. Ser Gln Asp Leu Ser Gly Gln Thr Ala Lys Lys Tyr Ala Val Ser Ser 15 20 25 Arg His Asn Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Xaa Lys Gln 35 40 Xaa Leu Lys Val Ser Ser Glu Asn Ser Asn Pro Xaa Gln Asp Leu Lys

50 Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Lys Gly Ser Glu Asn Ser Gln Pro Glu Glu Met Ser Gln Glu Pro Glu Ile Asn Xaa Gly Gly Asp 85 Arg Lys Val Glu Xaa Xaa Met Lys Lys His Gly Ser Xaa His Met Gly 100 105 Phe Pro Xaa Asn Leu Xaa Asn Gly Ala Thr Ala Asp Asn Gly Asp Asp 120 115 Gly Leu Ile Pro Pro Xaa Lys Xaa Xaa Thr Pro Glu Ser Xaa Gln Phe 135 130 Pro Asp Thr Glu Asn Glu Gln Tyr His Arg Asp Phe Ser Gly His Pro 145 150 Xaa Phe Pro Thr Thr Leu Pro Ile Lys Gln

<210> 492 <211> 216 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -15..-1

Met Val Cys Val Leu Val Leu Ala Ala Ala Ala Gly Ala Val Ala Val -5 -10 Phe Leu Ile Leu Arg Ile Trp Val Val Leu Arg Ser Met Asp Val Thr Pro Arg Glu Ser Leu Ser Ile Leu Val Val Ala Gly Ser Gly Gly His 25 Thr Thr Glu Ile Leu Arg Leu Leu Gly Ser Leu Ser Asn Ala Tyr Ser 40 45 Pro Arg His Tyr Val Ile Ala Asp Thr Asp Glu Met Ser Ala Asn Lys 55 60 Ile Asn Ser Phe Glu Leu Xaa Arg Xaa Asp Arg Xaa Pro Ser Asn Met 70 75 Xaa Thr Lys Tyr Tyr Ile His Arg Ile Pro Xaa Ser Arg Glu Val Gln 90 Gln Ser Trp Pro Ser Thr Val Xaa Thr Thr Leu His Ser Met Trp Leu 100 105 Ser Xaa Pro Leu Ile His Arg Val Lys Pro Xaa Leu Val Leu Cys Asn 120 125 Gly Pro Gly Thr Cys Val Pro Ile Cys Val Ser Ala Leu Leu Gly 140 135 Ile Leu Gly Ile Lys Lys Val Ile Ile Val Tyr Val Glu Ser Ile Cys 155 150 Arg Val Lys Thr Leu Ser Met Ser Gly Lys Ile Leu Phe His Leu Ser 170 Asn Tyr Phe Ile Val Gln Trp Pro Ala Leu Lys Glu Lys Tyr Pro Lys 185 Ser Val Tyr Leu Gly Arg Ile Val

<210> 493
<211> 134
<212> PRT

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<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 493
Met Pro Leu Gly Ala Arg Ile Leu Phe His Gly Val Phe Tyr Ala Gly
               -15
                                   -10
Gly Phe Ala Ile Val Tyr Tyr Leu Ile Gln Lys Phe His Ser Arg Thr
Leu Tyr Tyr Lys Leu Ala Val Glu Gln Leu Gln Xaa His Pro Glu Ala
                       20
                                           25
Gln Glu Ala Leu Gly Pro Pro Leu Asn Ile His Tyr Leu Lys Leu Ile
                  35
                                       40
Asp Arg Glu Asn Phe Val Asp Ile Val Xaa Ala Lys Leu Lys Ile Pro
         、 50
                                   55
Val Ser Gly Ser Lys Ser Glu Gly Leu Leu Tyr Val His Ser Ser Arg
           65
                               70
Gly Gly Pro Phe Gln Arg Trp His Leu Asp Glu Val Phe Leu Glu Leu
                           85
Lys Asp Gly Gln Gln Ile Pro Val Phe Lys Leu Ser Gly Glu Asn Gly
                       100
Asp Glu Val Lys Lys Glu
110
<210> 494
<211> 85
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
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<210> 495 <211> 292 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -29..-1

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<400> 495
Met His Gly Leu Leu His Tyr Leu Phe His Thr Arg Asn His Thr Phe
                                   -20
Ile Val Leu His Leu Val Leu Gln Gly Met Val Tyr Thr Glu Tyr Thr
                              - 5
Trp Glu Val Phe Gly Tyr Cys Gln Glu Leu Glu Leu Ser Leu His Tyr
                      10
                                          15
Leu Leu Leu Pro Tyr Leu Leu Gly Val Asn Leu Phe Phe Thr
                   25
                                      30
Leu Thr Cys Gly Thr Asn Pro Gly Ile Ile Thr Lys Ala Asn Glu Leu
                                  45
              40
Leu Phe Leu His Val Tyr Glu Phe Asp Glu Xaa Met Phe Pro Lys Asn
                              60
Val Arg Cys Ser Thr Cys Asp Leu Arg Lys Pro Ala Arg Ser Xaa His
                                              80
                          75
Cys Xaa Val Cys Asn Trp Cys Val His Arg Phe Xaa His His Cys Val
                      90
                                          95
Trp Val Asn Asn Cys Ile Gly Ala Trp Asn Ile Arg Xaa Phe Leu Ile
                  105
                                    110
Tyr Val Leu Thr Leu Thr Ala Ser Ala Ala Thr Val Ala Ile Val Ser
                                   125
              120
Thr Thr Phe Leu Val His Leu Val Val Met Ser Asp Leu Tyr Gln Glu
           135
                               140
Thr Tyr Ile Asp Asp Leu Gly His Leu His Val Met Asp Thr Val Phe
                           155
                                               160
Leu Ile Gln Tyr Leu Phe Leu Thr Phe Pro Arg Ile Val Phe Met Leu
                       170
                                           175
Gly Phe Val Val Val Leu Xaa Phe Leu Leu Gly Gly Tyr Leu Leu Phe
                   185
                                       190 <sub>.</sub>
Val Leu Tyr Leu Ala Ala Thr Asn Gln Thr Thr Asn Glu Trp Tyr Arg
               200
                                   205
Xaa Asp Trp Ala Trp Cys Gln Arg Cys Pro Leu Val Ala Trp Pro Pro
                              220
                                                   225
Ser Ala Glu Pro Gln Val His Arg Asn Ile His Ser His Gly Leu Arg
                          235
                                              240
Xaa Asn Leu Gln Glu Ile Phe Leu Pro Ala Phe Pro Cys His Glu Arg
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Lys Lys Gln Glu
260
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<210> 496 <211> 122 <212> PRT

<213> Homo sapiens

<220>
<221> SIGNAL
<222> -56..-1

<400> 496 Met Thr Gly Phe Leu Leu Pro Pro Ala Ser Arg Gly Thr Arg Arg Ser -50 -45 Cys Ser Arg Ser Arg Lys Arg Gln Thr Arg Arg Arg Arg Asn Pro Ser -35 -30 Ser Phe Val Ala Ser Cys Pro Thr Leu Leu Pro Phe Ala Cys Val Pro -20 -15 Gly Ala Ser Pro Thr Thr Leu Ala Phe Pro Pro Val Xaa Leu Thr Gly 1 Pro Xaa Thr Asp Gly Ile Pro Phe Ala Leu Xaa Ser Ala Ala Gly Pro 10 15 20

```
Phe Cys Ala Ser Phe Pro Ser Gly Xaa Leu Ser Pro Pro Gly Pro Leu 25 30 55 40

Pro Gly Val Arg Gly Leu Pro Leu Pro Ser Val Phe Tyr Ser Cys Gly 45 50 55

Ala His Pro Lys Val Leu Lys Val Ala Leu 60 65
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<210> 497 <211> 59 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28...1

<210> 498 <211> 99 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1

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<210> 499 <211> 99 <212> PRT <213> Homo sapiens

85

kaalistiin sitti ja ja aasaa ja jilkea ka kirikat etaki kaa askeesta kaa aasaa kaakistiin taa taa aa aa akki k

<220> -

<221> SIGNAL <222> -13..-1

<400> 499

Met His Leu Leu Ser Asn Trp Ala Asn Pro Ala Ser Ser Arg Arg Pro

Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu Ala His 5 10 15

Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys Trp Arg 20 25 30 35

Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn Ser Ser

Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr Pro Met 55 60 65

Arg Arg Ser Ser Cys His Leu Xaa Cys Gln Val Ile Phe Leu Leu Gly 70 75 80

Arg Gln Leu 85

<210> 500

<211> 108

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -25..-1

<400> 500

Met Ser Leu Thr Ser Ser Ser Ser Val Arg Val Glu Trp Ile Ala Ala
-25
-20
-15
-10

Val Thr Ile Ala Ala Gly Thr Ala Ala Ile Gly Tyr Leu Ala Tyr Lys

Arg Phe Tyr Val Lys Asp His Arg Asn Lys Ala Met Ile Asn Leu His

Ile Gln Lys Asp Asn Pro Lys Ile Val His Ala Phe Asp Met Glu Asp 25 30 35

Leu Gly Asp Lys Ala Val Tyr Cys Arg Cys Trp Arg Ser Lys Lys Phe 40 45 50 55

Pro Phe Cys Asp Gly Ala His Thr Lys His Asn Glu Glu Thr Gly Asp
60 65 70

Asn Val Gly Pro Leu Ile Ile Lys Lys Glu Thr 75 80

<210> 501

<211> 183

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -15..-1

<400> 501

Met Glu Ala Met Trp Leu Leu Cys Val Ala Leu Ala Val Leu Ala Trp

Gly Phe Leu Trp Val Trp Asp Ser Ser Glu Arg Met Lys Ser Arg Glu

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Gln Gly Arg Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala
                            25
His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu
                       40
                                           45
Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Gly Asn
                                        60
Tyr Tyr Asn Gln Gly Glu Thr Arg Lys Lys Glu Leu Leu Gln Ser Cys
                                    75
Asp Val Leu Gly Ile Pro Leu Ser Ser Val Met Ile Ile Asp Asn Arg
           85
                                90
Asp Phe Pro Xaa Asp Pro Gly Met Gln Trp Asp Thr Xaa His Val Ala
                            105
                                                110
Xaa Val Leu Leu Gln His Ile Glu Val Asn Gly Ile Asn Leu Val Val
                       120
                                            125
Thr Phe Asp Ala Gly Gly Xaa Ser Gly His Ser Asn His Ile Ala Leu
                   135
                                       140
Tyr Ala Ala Val Arg Lys Leu Glu Gly Gln Ile Cys Lys Pro Cys Gly
               150
Thr Gly Gln Asp Phe Lys Glu
            165
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<210> 502
<211> 98
<212> PRT
<213> Homo sapiens
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<222> -15..-1
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Met Glu Ala Met Trp Leu Leu Cys Val Ala Leu Ala Val Leu Ala Trp

<210> 503 <211> 183 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -57..-1

Xaa Ala

<400> 503
Met Asp Val Thr Gly Asp Glu Glu Glu Glu Ile Lys Gln Glu Ile Asn
-55
-50
-45

Met Leu Lys Lys Tyr Ser His His Arg Asn Ile Ala Thr Tyr Tyr Gly -35 -30 Ala Phe Ile Lys Lys Asn Pro Pro Gly Met Asp Asp Gln Leu Trp Leu -15 -20 Val Met Glu Phe Cys Gly Ala Gly Ser Val Thr Asp Leu Ile Lys Asn -5 Thr Lys Gly Asn Thr Leu Lys Glu Glu Trp Ile Ala Tyr Ile Cys Xaa 15 Glu Ile Leu Arg Gly Leu Xaa His Leu His Gln His Lys Val Ile His 30 35 Arg Xaa Ile Lys Gly Gln Asn Val Leu Leu Thr Glu Asn Ala Glu Val 45 50 Lys Leu Val Asp Phe Gly Xaa Xaa Ala Gln Leu Asp Arg Thr Val Gly 60 65 Arg Xaa Asn Thr Phe Ile Gly Thr Pro Tyr Trp Met Ala Pro Xaa Val 80 75 Ile Ala Cys Asp Glu Asn Pro Xaa Ala Thr Tyr Asp Phe Lys Xaa Asp 95 100 Leu Trp Ser Leu Gly Ile Thr Ala Ile Glu Met Ala Glu Gly Leu Pro 110 Leu Ser Val Thr Cys Thr Pro 125

<210> 504 <211> 140 <212> PRT <213> Homo sapiens

<220>
<221> SIGNAL
<222> -14..-1

<400> 504 Met Phe Leu Thr Ala Leu Leu Trp Arg Gly Arg Ile Pro Gly Arg Gln -10 -5 Trp Ile Gly Lys His Arg Arg Pro Arg Phe Val Ser Leu Arg Ala Lys 10 Gln Asn Met Ile Arg Arg Leu Glu Ile Glu Ala Glu Asn His Tyr Trp 25 30 Leu Ser Met Pro Tyr Met Thr Arg Glu Gln Glu Arg Gly His Ala Ala 45 40 Leu Arg Arg Glu Ala Phe Glu Ala Ile Lys Ala Ala Ala Thr Ser 55 60 Lys Phe Pro Pro His Arg Phe Ile Ala Asp Gln Leu Asp His Leu Asn 75 Xaa His Gln Glu Met Val Leu Ile Leu Ser Arg His Pro Trp Ile Leu 90 95 Trp Ile Thr Glu Leu Thr Ile Phe Thr Trp Ser Gly Leu Lys Asn Cys 105 110 Ser Leu Cys Glu Asn Glu Leu Trp Thr Ser Leu Tyr

120

<210> 505 <211> 59 <212> PRT <213> Homo sapiens

<220>

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<221> SIGNAL <222> -14..-1
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<400> 505

Met Ala Ala Leu Val Thr Val Leu Phe Thr Gly Val Arg Arg Leu His -10 -5

Cys Ser Ala Xaa Leu Gly Arg Ala Ala Ser Gly Xaa Tyr Ser Arg Asn 5 10 15

Trp Leu Pro Thr Pro Pro Ala Thr Gly Pro Leu Pro Ser Ser Gln Thr 20 25 30

Gly His Met Arg Met Ala Ala Leu Leu Pro Gln 35 40 45

<210> 506

<211> 101

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -36..-1

<400> 506

Met Gly Pro Tyr Asn Val Ala Val Pro Ser Asp Val Ser His Ala Arg
-35
-30
-25

Phe Tyr Phe Leu Phe His Arg Pro Leu Arg Leu Leu Asn Leu Leu Ile
-20 -15 -10 -5

Leu Ile Glu Gly Ser Val Val Phe Tyr Gln Leu Tyr Ser Leu Leu Arg
1 5 10

Ser Glu Lys Trp Asn His Thr Leu Ser Met Ala Leu Ile Leu Phe Cys
15 20 25

Asn Tyr Tyr Val Leu Phe Lys Leu Leu Arg Asp Arg Xaa Xaa Leu Gly 30 40

Arg Ala Tyr Ser Tyr Pro Leu Asn Ser Tyr Glu Leu Lys Ala Asn Xaa 45 50 55 60

Ala Ala Ser Xaa Gln

65

<210> 507

<211> 341

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -55..-1

<400> 507

Met Arg Lys Val Val Leu Ile Thr Gly Ala Ser Ser Gly Ile Gly Leu
-55 -45 -49

Ala Leu Cys Lys Arg Leu Leu Ala Glu Asp Asp Glu Leu His Leu Cys
-35
-25

-35 -30 -25 Leu Ala Cys Arg Asn Met Ser Lys Ala Glu Ala Val Cys Ala Ala Leu

 $^{\rm -20}$ $^{\rm -15}$ $^{\rm -10}$ Leu Ala Ser His Pro Thr Ala Glu Val Thr Ile Val Gln Val Asp Val

-5 1 5
Ser Asm Leu Gln Ser Phe Phe Arg Ala Ser Lys Glu Leu Lys Gln Arg
10 20 25

Phe Gln Arg Leu Asp Cys Ile Tyr Leu Asn Ala Gly Ile Met Pro Asn 35 Pro Gln Leu Asn Ile Lys Ala Leu Phe Phe Gly Leu Phe Ser Arg Lys 50 Val Ile His Met Phe Ser Thr Ala Glu Gly Leu Leu Thr Gln Gly Asp 65 Lys Ile Thr Ala Asp Gly Leu Gln Glu Val Phe Glu Thr Asn Val Phe 80 · 85 Gly His Phe Ile Leu Ile Arg Glu Leu Glu Pro Leu Cys His Ser 95 100 Asp Asn Pro Ser Gln Leu Ile Trp Thr Ser Ser Arg Ser Ala Arg Lys 120 115 110 Ser Asn Phe Ser Leu Glu Asp Phe Gln His Ser Lys Gly Lys Glu Pro 130 135 Tyr Ser Ser Ser Lys Tyr Ala Thr Asp Leu Leu Ser Val Ala Leu Asn 150 145 Arg Asn Phe Asn Gln Gln Gly Leu Tyr Ser Asn Val Ala Cys Pro Gly 160 165 Thr Ala Leu Thr Asn Leu Thr Tyr Gly Ile Leu Pro Pro Phe Ile Trp 180 175 Thr Leu Leu Met Pro Ala Ile Leu Leu Leu Arg Phe Phe Ala Asn Ala 190 195 Phe Thr Leu Thr Pro Tyr Asn Gly Thr Glu Ala Leu Val Trp Leu Phe 215 210 His Gln Lys Pro Glu Ser Leu Asn Pro Leu Ile Lys Tyr Leu Ser Ala 230 220 225 Thr Thr Gly Phe Gly Arg Asn Tyr Ile Met Thr Gln Lys Met Asp Leu 245 240 Asp Glu Asp Thr Ala Glu Lys Phe Tyr Gln Lys Leu Leu Glu Leu Glu 255 260 Lys His Ile Arg Val Thr Ile Gln Lys Thr Asp Asn Gln Ala Arg Leu 275 Ser Gly Ser Cys Leu

<210> 508 <211> 108 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -42..-1

<400> 508 Met His Ile Leu Gln Leu Leu Thr Thr Val Asp Asp Gly Ile Gln Ala -35 -30 Ile Val His Cys Pro Asp Thr Gly Lys Asp Ile Trp Asn Leu Leu Phe -20 -15 Asp Leu Val Cys His Glu Phe Cys Gln Ser Asp Asp Pro Ala Ile Ile -5 1 Leu Gln Xaa Gln Lys Thr Val Leu Ala Ser Val Phe Ser Val Leu Ser 15 10 Ala Ile Tyr Ala Ser Gln Thr Glu Gln Xaa Tyr Leu Lys Ile Xaa Lys 30 Gly Asp Gly Gly Ser Gly Ser Lys Gly Arg Pro Xaa Xaa Gln Thr Glu 45 50 Xaa Phe Leu Cys Ile Ser Lys Pro Ser Ser Phe Leu 60

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<210> 509
<211> 80
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<222> -26..-1
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Met Glu Glu Ile Ser Ser Pro Leu Val Glu Phe Val Lys Val Leu Cys
                       -20
Thr Asn Gln Val Leu Ile Thr Ala Arg Ala Val Pro Thr Lys Lys Ala
                   -5
                                       1
Ser Val Arg Cys Val Glu Lys Arg Phe Trp Ile Pro Lys Thr Thr Ser
          10
                               15
Lys His Leu Ser Arg Cys Ile Asp Gly Ile Ser Gly Phe Leu Asn Asp
                            30
                                               35
Phe Thr Phe Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu
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<210> 510
<211> 158
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -44..-1
<400> 510
Met Ala Gly Phe Leu Asp Asn Phe Arg Trp Pro Glu Cys Glu Cys Ile
                                    -35
Asp Trp Ser Glu Arg Arg Asn Ala Val Ala Ser Val Val Ala Gly Ile
           -25
                               -20
Leu Phe Phe Thr Gly Trp Trp Ile Met Ile Asp Ala Ala Val Val Tyr
                           -5
Pro Lys Pro Glu Gln Leu Asn His Ala Phe His Thr Cys Gly Val Phe
                  10
                                       15
Ser Thr Leu Ala Phe Phe Met Ile Asn Ala Val Ser Asn Ala Gln Val
               25
                                   30
Arg Gly Asp Ser Tyr Glu Ser Gly Cys Leu Gly Arg Thr Gly Ala Arg
                               45
Val Trp Leu Phe Ile Gly Phe Met Leu Met Phe Gly Ser Leu Ile Ala
                           60
                                               65
Ser Met Trp Ile Leu Phe Gly Ala Tyr Val Thr Gln Asn Thr Asp Val
                                           80
Tyr Pro Gly Leu Ala Val Phe Phe Gln Asn Ala Leu Ile Phe Phe Ser
                   90
Thr Leu Ile Tyr Lys Phe Gly Arg Thr Glu Glu Leu Trp Thr
               105
                                   110
<210> 511
<211> 130
<212> PRT
<213> Homo sapiens
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<220>
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<222> -28..-1

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<400> 511 Met Asn Trp Glu Leu Leu Trp Leu Leu Val Leu Cys Ala Leu Leu -25 -20 Leu Leu Val Gln Leu Leu Arg Phe Leu Arg Ala Asp Gly Asp Leu -5 -10 Thr Leu Leu Trp Ala Glu Trp Gln Gly Arg Arg Pro Glu Trp Glu Leu 15 10 Thr Asp Met Val Val Trp Val Thr Gly Ala Ser Ser Gly Ile Gly Glu 25 30 Glu Leu Ala Tyr Gln Leu Ser Lys Leu Gly Val Ser Leu Val Leu Ser 45 Ala Arg Arg Val His Glu Leu Glu Arg Val Lys Arg Arg Cys Leu Glu 65 60 Asn Gly Asn Leu Lys Glu Lys Asp Ile Leu Val Leu Pro Leu Asp Leu 75 80 Thr Asp Thr Gly Ser His Glu Ser Gly Tyr Gln Ser Cys Ser Pro Gly 90

<210> 512 <211> 199 <212> PRT <213> Homo sapiens

Ile Phe Lys Thr Lys His Asp

135

<220>
<221> SIGNAL
<222> -62..-1

<400> 512

Ile Trp

Met Ser Gln Arg Ser Leu Cys Met Asp Thr Ser Leu Asp Val Tyr Arg -55 -50 Xaa Leu Ile Glu Leu Asn Tyr Leu Gly Thr Val Ser Leu Thr Lys Cys -40 -35 Val Leu Pro His Met Ile Glu Arg Lys Gln Gly Lys Ile Val Thr Val -20 -15 -25 Asn Ser Ile Leu Gly Ile Ile Ser Val Pro Leu Ser Ile Gly Tyr Cys -5 -10 Ala Ser Lys His Ala Leu Arg Gly Phe Phe Asn Gly Leu Arg Thr Glu 5 10 Leu Ala Thr Tyr Pro Gly Ile Ile Val Ser Asn Ile Cys Pro Gly Pro 30 25 Val Gln Ser Asn Ile Val Glu Asn Ser Leu Ala Gly Glu Val Thr Lys 45 40 Thr Ile Gly Asn Asn Gly Asn Gln Ser His Lys Met Thr Thr Ser Arg 60 Cys Val Arg Leu Met Leu Ile Ser Met Ala Asn Asp Leu Lys Glu Val 70 75 Trp Ile Ser Glu Gln Pro Phe Leu Leu Val Thr Tyr Leu Trp Gln Tyr 90 Met Pro Thr Trp Ala Trp Trp Ile Thr Asn Lys Met Gly Lys Lys Arg 105 110 Ile Glu Asn Phe Lys Ser Gly Val Asp Ala Xaa Ser Ser Tyr Phe Lys 120 125

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<210> 513
<211> 180
<212> PRT
<213> Homo sapiens
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<222> -25..-1
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                                        -15
Ser Val Met Ala Ala Leu Thr Phe Gly Cys Phe Ile Xaa Thr Ala Phe
Lys Asp Arg Ser Val Pro Val Arg Leu His Val Ser Arg Ile Met Leu
                            15
Lys Asn Val Glu Asp Phe Thr Gly Pro Arg Glu Arg Ser Asp Leu Gly
                       30
Phe Ile Thr Phe Asp Ile Thr Ala Asp Leu Glu Asn Ile Phe Asp Trp
                   45
                                       50
Asn Val Lys Gln Leu Phe Leu Tyr Leu Ser Ala Glu Tyr Ser Thr Lys
               60
                                   65
Asn Asn Ala Leu Asn Gln Xaa Val Leu Trp Asp Lys Ile Val Leu Arg
Gly Asp Asn Pro Lys Leu Leu Lys Asp Met Lys Thr Lys Tyr Phe
                           95
Phe Phe Asp Asp Gly Asn Gly Leu Xaa Gly Asn Arg Asn Val Thr Leu
                       110
                                          115
Thr Leu Ser Trp Asn Val Val Pro Asn Ala Gly Ile Leu Pro Leu Val
                    125
                                       130
Thr Gly Ser Gly His Val Ser Val Pro Phe Pro Asp Thr Tyr Glu Ile
Thr Lys Ser Tyr
           155
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<210> 514 <211> 120 <212> PRT <213> Bos taurus

115

<400> 514

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 Met
 Thr
 Gly
 Arg
 Gln
 Gly
 Arg
 Ala
 Thr
 Phe
 Gln
 Phe
 Leu
 Pro
 Asp

 Glu
 Ala
 Arg
 Ser
 Leu
 Pro
 Pro
 Pro
 Lys
 Leu
 Thr
 Asp
 Pro
 Arg
 Leu
 Ala
 Ala
 Ile
 Asp
 Pro
 Arg
 Leu
 Ala
 Ile
 Arg
 Arg
 Arg
 Pro
 Val
 Leu
 Leu
 Ala
 Gly
 Leu
 His
 Arg
 Gln
 Leu
 Leu
 Tyr
 Tyr
 Tyr
 Leu
 His
 Arg
 Gln
 Leu
 Leu
 Tyr
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 Tyr
 Leu

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<211> 1082
<212> DNA
<213> Homo sapiens
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                                                                  120
cgcagcccga agattcacta tggtgaaaat cgccttcaat acccctaccg ccgtgcaaaa
                                                                  180
ggaggaggcg cggcaagacg tggaggccct cctgagccgc acggtcagaa ctcagatact
                                                                  240
                                                                  300
gaccggcaag gagctccgag ttgccaccca ggaaaaagag ggctcctctg ggagatgtat
                                                                  360
gettactete ttaggeettt catteatett ggeaggaett attgttggtg gageetgeat
                                                                  420
ttacaagtac ttcatgccca agagcaccat ttaccgtgga gagatgtgct tttttgattc
tgaggatect gcaaattece ttegtggagg agagectaae tteetgeetg tgaetgagga
                                                                  480
                                                                  540
ggctgacatt cgtgaggatg acaacattgc aatcattgat gtgcctgtcc ccagtttctc
                                                                  600
tgatagtgac cctgcagcaa ttattcatga ctttgaaaag ggaatgactg cttacctgga
                                                                  660
cttgttgctg gggaactgct atctgatgcc cctcaatact tctattgtta tgcctccaaa
aaatctggta gagctctttg gcaaactggc gagtggcaga tatctgcctc aaacttatgt
                                                                  720
ggttcgagaa gacctagttg ctgtggagga aattcgtgat gttagtaacc ttggcatctt
                                                                  780
tatttaccaa ctttgcaata acagaaagtc cttccgcctt cgtcgcagag acctcttgct
                                                                  840
gggtttcaac aaacgtgcca ttgataaatg ctggaagatt agacacttcc ccaacgaatt
                                                                  900
tattgttgag accaagatct gtcaagagta agaggcaaca gatagagtgt ccttggtaat
                                                                  960
aagaagtcag agatttacaa tatgacttta acattaaggt ttatgggata ctcaagatat
                                                                 1020
1080
                                                                 1082
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<211> 559
<212> DNA
<213> Homo sapiens
<400> 516
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aggetggccg agetgcaggc caaacacggg gatcetggtg atgeggccca acaggaagca
                                                                  120
aagcacaggg aagcagaaat gagaaacagt atcttagccc aagttctgga tcagtcggcc
                                                                  180
cgggccaggt taagtaactt agcacttgta aagcctgaaa aaactaaagc agtagagaat
                                                                  240
taccttatac agatggcaag atatggacaa ctaagtgaga aggtatcaga acaaggttta
                                                                  300
                                                                  360
atagaaatcc ttaaaaaagt aagccaacaa acagaaaaga caacaacagt gaaattcaac
agaagaaaag taatggactc tgatgaagat gacgattatt gaactacaag tgctcacaga
                                                                  420
                                                                  480
ctagaactta acggaacaag tctaggacag aagttaagat ctgattattt actttgttta
                                                                  540
559
aaaaaaaaa aaaaaaaaa
<210> 517
<211> 110
<212> PRT
<213> Homo sapiens
<400> 517
Met Phe Cys Pro Leu Lys Leu Ile Leu Leu Pro Val Leu Leu Asp Tyr
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Ser Leu Gly Leu Asn Asp Leu Asn Val Ser Pro Pro Glu Leu Thr Val
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His Val Gly Asp Ser Ala Leu Met Gly Cys Val Phe Gln Ser Thr Glu
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